December 18, 1998

This document was submitted to EPA by a registrant in connection with EPA's evaluation of this chemical and it is presented here exactly as submitted.

13/099#

239 (P)

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Hand Delivered

November 6, 1998

Ms. Emily Mitchell
Case Manager
Reregistration Branch I
Special Review and Reregistration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Crystal Mall 2, Room 657
1921 Jefferson Davis Highway
Arlington, VA 22202

Dear Ms. Mitchell:

This letter is submitted on behalf of Cheminova Agro A/S and concerns the Office of Pesticide Programs' preliminary human health risk assessment for methyl parathion, including the draft Health Effects Division Reregistration Eligibility Decision (RED) document chapter. In response to Arnold Layne's October 6, 1998, letter (that we received on October 7, 1998), we are submitting comments on these draft documents, as well as on the issues concerning methyl parathion included in the July 7, 1998, HIARC document entitled "Hazard Assessment of the Organophosphates."

Three copies of the following data and information (all formatted per PR Notice 86-5) are being submitted:

VOLUME #	GUIDELINE #	MRID	TITLE
I	not applicable		Comments on EPA's Methyl Parathion Draft Health Effects Division Chapter of the Reregistration Eligibility Decision Document (with the following attachments:) Attachment A: Cheminova's comments on EPA's *Toxicology Chapter* (Kathleen Raffaele, March 10, 1998) (EPA Attachment 2)

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VOLUME #	GUIDELINE #	MRID	TITLE
			Attachment B: Cheminova's comments on the Agency document titled *Methyl Parathion (O,O-dimethyl O-p-nitrophenyl phosphorothioate): Hazard Identification Committee Report* (George Ghali, December 1, 1997) (EPA Attachment 1) Attachment C: Cheminova's comments with respect to methyl parathion on a draft report from EPA's Hazard Identification Assessment Review Committee (HIARC) titled *Hazard Assessment of the Organophosphates* (dated July 7, 1998) and a combined report from the Food Quality Protection act (FQPA) Safety Factor Committee and the HIARC, titled *FQPA Safety Factor Recommendations for the Organophosphates* (dated August 6, 1998) Attachment D: Cheminova's comments on EPA's *Residue Chemistry Chapter for the Methyl Parathion Reregistration Eligibility Decision (RED) Document* (Bonnie Cropp-Kohlligian, June 11, 1998) Attachment E: Cheminova's comments on EPA's document titled *Methyl Parathion. The Outcome of the HED Metabolism Assessment Review Committee Meeting Held on March 11, 1998* (Bonnie Cropp-Kohlligian, May 21, 1998) (EPA Attachments 3 and 4) Attachment F: Cheminova's comments on EPA's *Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Methyl Parathion* (Johathan Becker, March 2, 1998)

VOLUME #	GUIDELINE #	MRID	TITLE
			Attachment G: A list of the references used by Cheminova in compiling these comments, including public literature, EPA memoranda, and EPA Data Evaluation Records (DERs). Attachment H: **CONFIDENTIAL ATTACHMENT** - This attachment has sales information on methyl parathion and has been removed from the releasable part of this document.
II	81-2		Dreher, D.M. (1993) "Acute Dermal Toxicity Test in the Rat." Safepharm Laboratories Limited. Project No. 545/8.
III	81-1		Dreher, D.M. (1993) "Acute Oral Toxicity Test in the Rat." Safepharm Laboratories Limited. Project No. 545/7.
IV	not applicable		English Translation of Fuchs, V., Golbs, S., Kuhnert, M., and Osswald, F. (1976) "Studies on the Prenatal Toxic Activity of Methyl Parathion on Wistar Rats in Comparison to Cyclophosphamide and Trypan Blue." *Archives of Experimental Veterinary Medicine (Leipzig)*, 30 (May 3), 343-350.
V	83-3		Hoberman, A. M. (1991) "Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of Methyl Parathion Technical Administered Orally Via Stomach Tube to New Zealand White Rabbits." Argus Research Laboratories, Inc. Report No. 310-007.
VI	not applicable		Kumar, K.B., Devi, K.S. (1996) "Methyl Parathion Induced Teratological Study in Rats." *Journal Environmental Biology*, 17 (1), 51-57.
VII	83-4		Löser, E., and Eiben, R. (1982) "E 605-Methyl Multigeneration Studies on Rats." Bayer AG Institute of Toxicology. Report No. 10630.

As requested, we are also enclosing an electronic copy of our comments (Volume I from the table above).

We have reviewed the draft Agency documents for possible Confidential Business Information (CBI) and have not identified anything that we consider to be CBI. Likewise, we have considered our own comments and the other documents we are submitting (identified above) for possible CBI. The documents we are submitting have all been formatted according to PR Notice 86-5 (in anticipation of receiving an MRID number for each document) and, thus, any CBI has been identified and handled according to the PR Notice. Further, throughout our comments we have identified additional testing we have planned or have underway. As soon as we have completion dates, we will inform you of our target submission dates for these studies. Lastly, on pages x-y of our comments, we have identified the errors in EPA's documents that should be corrected before the documents are released for public comment.

We appreciate the effort the Agency staff has put into preparing this draft RED chapter and we welcome the opportunity to comment on it. We request a reasonable period of time to review the methyl parathion docket prior to its public release. We consider this submission a continuation of our dialogue with the Agency on the reregistration of methyl parathion and believe the next best step may be a meeting with you and the other methyl parathion team members to discuss our comments. Please do not hesitate to call me (703-312-8520) if you have any comments about our comments or the other documents in this submission.

Sincerely,

Diane Allemang
Jellinek, Schwartz & Connolly, Inc.
Authorized Representative of
Cheminova Agro A/S

Enclosures

cc: David Menotti, Shaw Pittman
Don O'Shaughnessy, Cheminova Inc.
Jon Weis, Cheminova Agro A/S

STUDY TITLE

Comments on EPA's Methyl Parathion
Draft Health Effects Division Chapter
of the Reregistration Eligibility Decision Document

DATA REQUIREMENTS

Not Applicable

AUTHOR(S)

Cheminova Agro A/S
P.O. Box 9, DK-7620
Lemvig, Denmark

PERFORMING LABORATORY

Not Applicable

REPORT COMPLETION DATE

November 6, 1998

SUBMITTER

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SPONSOR'S REPRESENTATIVE

Jellinek, Schwartz & Connolly, Inc.
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Arlington, VA 22209

REPORT NUMBER

Not Applicable

STATEMENT OF DATA CONFIDENTIALITY CLAIMS

Information claimed confidential on the basis of its falling within the scope of FIFRA ' 10 has been removed to a confidential attachment, and is cited by cross-reference number in the body of the study.

Company: Cheminova Agro A/S

Company Agent: Jon Weis

Title: Manager, Patents and Registration

Signature: _____ Date: _____

These data are the property of Cheminova Agro A/S and as such, are considered to be confidential for all purposes other than compliance with FIFRA ' 10. Submission of these data in compliance with FIFRA does not constitute a waiver of any right to confidentiality which may exist under any other statute or in any other country.

CERTIFICATION OF GOOD LABORATORY PRACTICE

This report is a response to EPA's draft Health Effects Division Chapter of the Reregistration Eligibility Decision Document for methyl parathion. As such, Good Laboratory Practice Standards (40 CFR Part 160) are not applicable to this submission.

Submitter: _____ Date: _____

Diane Allemang
Jellinek, Schwartz & Connolly, Inc.
Authorized Representative for
Cheminova Agro A/S

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Attachments

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Attachment F: Cheminova's comments on EPA's *Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Methyl Parathion* (Jonathan Becker, March 2, 1998)

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Attachment H: **CONFIDENTIAL ATTACHMENT** – This attachment has sales information on methyl parathion and has been removed from the releasable part of this document.

EXECUTIVE SUMMARY

Cheminova Agro A/S (Cheminova) is respectfully submitting these comments on EPA's draft Health Effects Division (HED) chapter of the Reregistration Eligibility Decision (RED) Document on methyl parathion. The draft HED chapter is comprised of a memorandum titled "Methyl Parathion. The HED Chapter of the Reregistration Eligibility Decision Document (RED)" (Diana Locke, September 1, 1998) (herein referred to as the HED Chapter), and the following seven attachments to the HED Chapter:

- Attachment 1: "Methyl Parathion (O,O-dimethyl O-p-nitrophenyl phosphorothioate): Hazard Identification Committee Report" (George Ghali, December 1, 1997);

- Attachment 2: "Toxicology Chapter" (Kathleen Raffaele, March 10, 1998);

- Attachment 3: "Residue Chemistry Chapter for the Methyl Parathion Reregistration Eligibility Decision (RED) Document" (Bonnie Cropp-Kohlligian, June 11, 1998);

- Attachment 4: "Methyl Parathion (053501). The Outcome of the HED Metabolism Assessment Review Committee Meeting Held on March 11, 1998" (Bonnie Cropp-Kohlligian, May 21, 1998);

- Attachment 5: "DEEM Results" (Richard Griffin, August 11, 1998);

- Attachment 6: "Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Methyl Parathion" (Jonathan Becker, March 2, 1998); and

- Attachment 7: "Review of Methyl Parathion Incident Reports" (Jerome Blondell/Monica Spann, February 5, 1998).

Cheminova is addressing the information presented in the Agency's documents regarding toxicology, residue chemistry, metabolism, and occupational exposure. Cheminova is also commenting on a draft report from EPA's Hazard Identification Assessment Review Committee (HIARC) titled "Hazard Assessment of the Organophosphates" (dated July 7, 1998) and a combined report from the Food Quality Protection Act (FQPA) Safety Factor Committee and the HIARC, titled "FQPA Safety Factor Recommendations for the Organophosphates" (dated August 6, 1998).

Cheminova is one of only two sources of technical methyl parathion registered in the United States. Although Cheminova believes that the technical methyl parathion sold by Griffin Corporation (Griffin) is from an alternative source, Griffin's registration is based on citations of Cheminova's data. Because Griffin is relying on Cheminova's data to support its technical registration, Cheminova believes that Cheminova's decisions regarding the supported uses for

methyl parathion should be regarded as applicable to all other manufacturing use and end-use registrations unless others (e.g., other registrants, IR-4) are willing to develop their own supporting data.

Cheminova disagrees with the Agency's selection of endpoints of concern for acute and chronic dietary and short- and intermediate-term occupational risk assessments. Cheminova believes that the Agency failed to consider certain key data, misinterpreted various study results, and, therefore, selected inappropriate endpoints that exaggerate the potential risk posed by the use of methyl parathion. Cheminova provides a detailed rationale for selecting endpoints that are conservative but that fully and accurately consider EPA's database of existing toxicology data on methyl parathion. Risk assessments conducted using Cheminova's proposed endpoints would provide a more realistic prediction of potential risk and would substantially reduce EPA's concerns. Moreover, Cheminova is conducting additional toxicology studies on methyl parathion, which should provide a basis for further refining the acute dietary and short-term dermal methyl parathion hazard and risk assessments.

Cheminova disagrees with EPA's conclusion that retention of the FQPA safety factor for methyl parathion is warranted for protection of infants and children. EPA based this decision on increased pup susceptibility compared with adults and neuropathology seen "at [a] low dose level" in the acute neurotoxicity test. Cheminova believes that the available data for methyl parathion, which constitute a complete and acceptable database, fail to provide evidence of pup susceptibility except at extremely high dose levels by inappropriate routes of administration, and do not show evidence of neuropathological effects at low dose levels.

EPA further concludes that retention of the FQPA safety factor for methyl parathion is necessary based on the absence of a developmental neurotoxicity study. Cheminova believes that this study is unnecessary; as demonstrated by a weight-of-the-evidence assessment, in which the greatest weight is given to modern, Guideline studies. EPA did not conduct such an assessment but instead relied upon weak and inappropriate studies in the public literature. Even if the requirement for the study is justified, the absence of this study should not be used as rationale for imposing an additional safety factor.

In the occupational exposure assessment results presented in the draft HED chapter, EPA calculated margins of exposure (MOEs) for use patterns and exposure scenarios that are not being supported for reregistration. For use patterns that Cheminova is supporting, a clarification of key modeling inputs (including required personal protective equipment, engineering controls, reentry intervals, supported formulations, supported application methods, and supported uses) should reduce EPA's concerns.

Furthermore, Cheminova believes that EPA mistakenly includes an additional 10X safety factor in its occupational exposure risk assessment. Cheminova notes that the September 1, 1998, draft HED chapter states that the extra 10X is not necessary for occupational exposure and risk assessments. Cheminova also believes that EPA further overestimated occupational exposure by applying a 100% default value for dermal absorption to all dermal exposure

scenarios because it lacks confidence in a much lower dermal absorption value predicted by a 28-day rabbit study. Cheminova believes that the Agency's use of the default value is unduly conservative. Other rat *in vitro* and *in vivo* data are available which estimate dermal absorption for the technical or formulated product to be in the 10% to 25% range. Cheminova is conducting a new dermal study that will definitively resolve this issue; in the interim, a default value of 25% is appropriate.

EPA states that its risk estimates indicate that acute and chronic dietary risks from methyl parathion are of concern. This conclusion, however, is based only on results of Tier I dietary exposure assessments. EPA's policy (Acute Dietary Exposure Assessment Office Policy, [1996] and Draft Office of Pesticide Programs Policy for the Use of Anticipated Residues for Pesticides in Foods in Chronic Dietary Exposure Assessment [1997]) is that dietary risk assessments should be conducted using a tiered approach, using increasingly more realistic assumptions. Cheminova believes that EPA should clarify in the HED Chapter that Tier I results mean only that a more realistic assessment of the risk should be conducted using higher-tier assessment procedures. Cheminova believes that higher-tier assessments will show more acceptable MOEs for methyl parathion.

Cheminova's comments on each of EPA's attachments are provided as attachments to this document as follows:

- **Attachment A** – Cheminova's comments on EPA's *Toxicology Chapter* (Kathleen Raffaele, March 10, 1998) (EPA Attachment 2);

- **Attachment B** – Cheminova's comments on the Agency document titled *Methyl Parathion (O,O-dimethyl O-p-nitrophenyl phosphorothioate): Hazard Identification Committee Report* (George Ghali, December 1, 1997) (EPA Attachment 1);

- **Attachment C** – Cheminova's comments with respect to methyl parathion on a draft report from EPA's Hazard Identification Assessment Review Committee (HIARC) titled *Hazard Assessment of the Organophosphates* (dated July 7, 1998) and a combined report from the Food Quality Protection act (FQPA) Safety Factor Committee and the HIARC, titled *FQPA Safety Factor Recommendations for the Organophosphates* (dated August 6, 1998);

- **Attachment D** – Cheminova's comments on EPA's *Residue Chemistry Chapter for the Methyl Parathion Reregistration Eligibility Decision (RED) Document* (Bonnie Cropp-Kohlligian, June 11, 1998);

- **Attachment E –** Cheminova's comments on EPA's document titled *Methyl Parathion. The Outcome of the HED Metabolism Assessment Review Committee Meeting Held on March 11, 1998* (Bonnie Cropp-Kohlligian, May 21, 1998) (EPA Attachments 3 and 4);

- **Attachment F** – Cheminova's comments on EPA's *Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Methyl Parathion* (Jonathan Becker, March 2, 1998);

- **Attachment G** – A list of the references used by Cheminova in compiling these comments, including public literature, EPA memoranda, and EPA Data Evaluation Records (DERs), is provided in Attachment G; and

- **Attachment H** – This attachment is **CONFIDENTIAL** because it contains sales information on methyl parathion; thus, it has been removed from the releasable part of this document.

I. INTRODUCTION

Cheminova Agro A/S (Cheminova) is respectfully submitting these comments on EPA's draft Health Effects Division (HED) chapter of the Reregistration Eligibility Decision (RED) Document on methyl parathion. The draft HED chapter is comprised of a memorandum titled "Methyl Parathion. The HED Chapter of the Reregistration Eligibility Decision Document (RED)" (Diana Locke, September 1, 1998) (herein referred to as the "HED Chapter") and seven attachments. Cheminova is also providing comments at this time with respect to methyl parathion on a draft report from EPA's Hazard Identification Assessment Review Committee (HIARC) titled "Hazard Assessment of the Organophosphates" (dated July 7, 1998) and a combined report from the Food Quality Protection Act (FQPA) Safety Factor Committee and the HIARC, titled "FQPA Safety Factor Recommendations for the Organophosphates" (dated August 6, 1998).

Methyl parathion, a broad spectrum insecticide for use on a variety of agricultural crops, has been used world wide for more than 40 years. Cheminova has a long track record of compliance with all federal testing and labeling requirements for methyl parathion and its other pesticide products. Over the past several years, Cheminova has conducted and submitted many studies to fully define the toxicity of methyl parathion. These studies have all been submitted to the Office of Pesticide Programs, in accordance with EPA's schedule for data submission, to support the registration of Cheminova's technical methyl parathion. Further, Cheminova worked with the Agency to minimize potential risk posed by the use of methyl parathion. Cheminova fully cooperated with EPA's initiative to reduce the chance of illegal misuse, by agreeing to and implementing formulation and packaging changes.

Cheminova's comments provide EPA with additional information about methyl parathion and its supported use patterns. This additional information should enable the Agency to conduct a more accurate assessment of the potential risk to human health than is presented in the draft HED RED chapter. Cheminova's comments address the following subjects: (1) the uses and use patterns that Cheminova and Elf Atochem North America, Inc. (Elf Atochem) will support for reregistration; (2) toxicology; (3) dietary exposure; (4) metabolism; and (5) occupational exposure.

Finally, Cheminova adopts and incorporates by reference in these comments the document titled "*A Science-Based, Workable Framework for Implementing the Food Quality Protection Act*" (Implementation Working Group (IWG), June 1998), which the IWG has submitted to EPA.

II. CHEMINOVA'S COMMENTS ON ERRORS

In the October 6, 1998, cover letter from Arnold Layne that accompanied EPA's draft HED chapter for the methyl parathion RED, the Agency requested that Cheminova limit its comments in the 30-day period to comments on errors including, but not limited to, "mathematical, computational, typographic, or other similar errors". Listed below are the errors of this sort that Cheminova has identified within the draft HED chapter. Cheminova believes that there are many more "errors" that do not fit EPA's restrictive definition, such as errors in applicability of data and flaws in data analysis. These types of errors are identified later in this document.

A. ERRORS: USE PATTERNS FOR METHYL PARATHION

EPA states that Cheminova and Elf Atochem are the only two basic producers of methyl parathion in the United States. Elf Atochem is not a basic producer of methyl parathion, it is a formulator. However, Cheminova notes that EPA recently approved a registration of a second source of technical methyl parathion. The new technical registrant is Griffin Corporation (Griffin).

EPA states that methyl parathion may be applied by chemigation. Cheminova is not supporting the application of the emulsifiable concentrate (EC) formulation of methyl parathion through any type of irrigation device. The labels for Cheminova's and Griffin's end-use products include language that specifically prohibits chemigation. EPA should specify that it is only Elf Atochem's end-use label that currently allows the microencapsulated (Mcap) formulation to be applied using chemigation.

EPA states that methyl parathion may be applied by tractor-drawn granular spreaders. Cheminova is not supporting registration of granular formulations; therefore, application via tractor-drawn granular spreader should not be included in the Agency's risk assessments.

EPA claims that commercial applicators could potentially apply methyl parathion to fruit trees in residential settings and requests that the labels be amended to specifically prohibit such use. This statement by the Agency is erroneous. There are no legal residential uses for methyl parathion. In fact, Cheminova's technical label states that the technical material may be formulated only into formulations for use on "terrestrial, nondomestic, food uses" and "terrestrial, nondomestic, nonfood uses." Further, Cheminova's end-use label states that methyl parathion is "not for use in or around the home." Cheminova believes that use in residential settings is a violation of language already on its labels and therefore would constitute an illegal misuse of the product. If other registrants hold labels that allow such a use, EPA should

require these registrants to amend their labels to specifically prohibit any such residential uses.

Cheminova notes that EPA erroneously included kohlrabi in its dietary risk assessments. The use of methyl parathion on kohlrabi is not being supported, as was noted in Cheminova's and Elf Atochem's 90-day responses to the April 10, 1997, data call-in (DCI).

B. ERRORS: HED CHAPTER (SEPTEMBER 1, 1998)

The use pattern errors identified above should be reviewed with respect to the risk assessment results presented in the September 1, 1998, memorandum.

Cheminova believes that the Agency incorrectly presented the results of EPA's acute dietary assessments as percentages of the acute reference dose (RfD) (on pages 1 and 10) without making clear what additional safety factors have been included in the calculations. Previous EPA guidance states that acute risk assessment results are to be presented as margins of exposure (MOEs), based on the no-observed-effect-level (NOEL), not the RfD. Expression of the risk as a percentage of the RfD could lead to confusion because the safety factors are included in the RfD.

On page 12, EPA states that a new lettuce metabolism study is required. Cheminova notes that the requested lettuce metabolism study was submitted on October 9, 1998 (MRID 44669501). While this study was submitted after EPA's draft HED chapter was completed, Cheminova requests that EPA recognize the submission of this report in the RED.

On page 12, EPA states that additional data are required to validate the experimental methods for the poultry and ruminant metabolism studies. Cheminova notes that it submitted the requested data and information needed to validate the poultry and ruminant metabolism studies on February 2, 1998 (no MRID number was assigned to this submission). Cheminova requests that EPA note that the data and information have been submitted.

On page 12, EPA provides a list of crops/commodities for which field trial data are required. Cheminova notes that neither it or Elf Atochem is supporting the use of methyl parathion on sorghum forage and rape forage; these crops are incorrectly included in EPA's list.

C. ERRORS: TOXICOLOGY CHAPTER (MARCH 10, 1998)

Although not errors as defined in the cover letter from EPA providing the Toxicology Chapter, the following items appear to be errors that the Agency should be aware of:

1. EPA misreports the results of the study by Fuchs *et al.* (1975). The EPA summary appears to be based on the translated abstract of this German study, and not on the actual study report. The specific errors are discussed in Attachment A.

2. EPA misreports the results of the study by Kumar and Devi (1996) and Gupta *et al*. (1985). The specific errors are discussed in Attachment A.

3. There are errors in the Agency's summary of findings from the acute neurotoxicity study. The specific errors are discussed in Attachment A.

4. There are misstatements and errors in the Agency's summary of findings from the subchronic neurotoxicity study. The specific errors are discussed in Attachment A.

D. ERRORS: HID DOCUMENT (DECEMBER 1, 1997)

1. EPA misreports the results of the study by Fuchs *et al.* (1975). The EPA summary appears to be based on the translated abstract of this German study, and not on the actual study report. The specific errors are discussed in Attachment B.

2. EPA misreports the results of the study by Kumar and Devi (1996) and Gupta *et al*. (1985). The specific errors are discussed in Attachment B.

3. There are errors in the Agency's summary of findings from the acute neurotoxicity study. The specific errors are discussed in Attachment B.

4. There are misstatements and errors in the Agency's summary of findings from the subchronic neurotoxicity study. The specific errors are discussed in Attachment B.

E. ERRORS: RESIDUE CHAPTER (JUNE 11, 1998)

1. In the second sentence of the introduction of the Residue Chemistry chapter (page 2), the word "respectively" should be added because Cheminova's product is called Methyl Parathion 4EC and Elf Atochem's product is called Penncap-M®.

2. In the section titled "Nature of the Residue in Plants" (page 5), EPA states that a new lettuce metabolism study is required. Cheminova notes that it submitted the new lettuce metabolism study to EPA on October 9, 1998 (MRID 44669501). Cheminova requests that EPA acknowledge the receipt of the new study in the RED.

3. In the section titled "Nature of the Residue in Livestock" (page 6), EPA requests submission of additional information and data to validate the experimental methods for the poultry and ruminant metabolism studies. Cheminova notes that it submitted the requested information to EPA in a letter dated February 2, 1998 (no MRID number was assigned to this submission). Cheminova requests that EPA acknowledge the receipt of the requested information in the RED.

4. On page 7 in the section titled "Residue Analytical Methods," EPA states that the RED indicates that all of the residue data on crop and processed commodities were collected using a modification of Elf Atochem Method Number BR-007-00. That statement is an error. The studies conducted by Cheminova did not use the Elf Atochem analytical method. As stated in the Agency's Methyl Parathion Residue Chemistry Reregistration Standard Update (November 20, 1992), the Cheminova study samples were analyzed using a modification of method I(a) from Pesticide Analytical Manual (PAM), Volume II.

5. On page 9, EPA states that for the purposes of reregistration, aspirated grain fractions (AGF) data are required. Cheminova notes that the April 10, 1997, DCI requested AGF data only for wheat. Cheminova is currently conducting this study.

6. On page 9, EPA states that residue data are required for sweet potatoes. In Table B (page 36), EPA contradicts itself by stating that it will translate potato residue data to support sweet potatoes. Cheminova is not supporting the use of the EC formulation on sweet potatoes. However, Elf Atochem is supporting a 24(c) registration of the Mcap formulation on this crop.

7. On page 9, EPA states that IR-4 plans to support the use of methyl parathion on hops. Cheminova understands that IR-4 also plans to support the use of methyl parathion on bell peppers and melons.

F. ERRORS: METABOLISM (MAY 21, 1998)

1. EPA requests that analyses of samples in future plant and animal magnitude of the residue studies include paranitrophenol (PNP), so that aggregate exposure from all registered uses of PNP can be evaluated. This request is erroneous, because the sole registrant of PNP, the United States Department of the Army, has requested the cancellation of the registration of this compound (January 1998 PNP RED).

G. ERRORS: OCCUPATIONAL EXPOSURE (MARCH 2, 1998)

1. Cheminova believes that EPA has erroneously included the term "residential" in the title of this chapter: Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Methyl Parathion. Because there are no residential uses for methyl parathion, EPA should not include "residential" in the title.

2. EPA erroneously applied an additional 10X FQPA safely factor to its occupational risk assessments. EPA's September 1, 1998, draft HED chapter specifically states that this additional 10X safety factor is not required for occupational risk assessments. In addition, EPA's "Special Report of the FQPA Safety Factor Committee" (April 15, 1998) states that the Agency does not consider it appropriate to apply an FQPA safety factor to occupationally exposed workers.

3. In EPA's Tables 2 and 3, Exposure Scenario 7 is listed as applying liquids using an airblast sprayer. Cheminova notes that the airblast sprayer application method is supported only for the Mcap formulation. Cheminova requests that the Agency clarify this by adding the term "microencapsulated" to Scenario 7 in these Tables.

4. In EPA's Table 5, the second of the two column subheadings under the heading "Dermal Dose" should be "Max Rate", not "Min Rate".

5. Footnote C of EPA's Table 5 is inconsistent with the text and table calculation. The maximum rate should be 20,000 cm^2/hr, not 10,000 cm^2/hr.

5. EPA calculated the MOEs for exposure scenarios that are no longer supported. A clarification of key modeling inputs (including required personal protective equipment, engineering controls, reentry intervals, supported formulations, supported application methods, and supported uses) is provided in Attachment F, Section V.

III. CHEMINOVA'S COMMENTS ON CONFIDENTIAL BUSINESS INFORMATION (CBI)

Cheminova has reviewed the Agency documents for possible Confidential Business Information (CBI) and has not identified anything that it considers to be CBI. Likewise, Cheminova has considered its own comments and the other documents it is submitting (identified below) for possible CBI. The documents Cheminova is submitting have all been formatted according to PR Notice 86-5 (in anticipation of receiving an MRID number for each document) and, thus, any CBI has been identified and handled according to the PR Notice.

In Section VII. of this document (Section VII. E. Use of Methyl Parathion in the United States), Cheminova has removed to a Confidential Attachment (Attachment H) financial information on methyl parathion.

IV. STUDIES BEING SUBMITTED WITH CHEMINOVA'S COMMENTS

Cheminova has identified certain studies that it is submitting along with this document and its attachments. These studies are identified below. Each of these studies has been formatted according to PR Notice 86-5.

Hoberman, A. M. (1991) "Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of Methyl Parathion Technical Administered Orally Via Stomach Tube to New Zealand White Rabbits." Argus Research Laboratories, Inc. Report No. 310-007.

Löser, E., and Eiben, R. (1982) "E 605-Methyl Multigeneration Studies on Rats." Bayer AG Institute of Toxicology. Report No. 10630.

Dreher, D.M. (1993) "Acute Dermal Toxicity Test in the Rat." Safepharm Laboratories Limited. Project No. 545/8.

Dreher, D.M. (1993) "Acute Oral Toxicity Test in the Rat." Safepharm Laboratories Limited. Project No. 545/7.

English translation of Fuchs, V., Golbs, S., Kuhnert, M., and Osswald, F. (1976) "Studies on the Prenatal Toxic Activity of Methyl Parathion on Wistar Rats in Comparison to Cyclophosphamide and Trypan Blue." *Archives of Experimental Veterinary Medicine (Leipzig)*, 30 (May 3), 343-350.

Kumar, K.B., Devi, K.S. (1996) "Methyl Parathion Induced Teratological Study in Rats." *Journal Environmental Biology*, 17 (1), 51-57.

V. STUDIES CHEMINOVA WILL SUBMIT DURING THE 60-DAY COMMENT PERIOD

Identified below are the studies that Cheminova intends to submit during the 60-day comment period for the draft methyl parathion HED chapter of the RED. Each of these studies will be formatted according to PR Notice 86-5.

Valdez-Flores, C. (1998) "Statistical Reanalysis on a Per Litter Basis on Data from 'E-605-methyl. Multigeneration Studies on Rats' (E. Löser and R. Eiben, 1982, Bayer AG Report No. 10630)." Sielken, Inc.

B. Valdez-Flores, C. (1998) "Statistical Reanalysis on a Per Litter Basis on Data from 'A Two-Generation Reproduction Study of Methyl Parathion in Rats' (I.W. Daly and G.K. Hogan, 1982, Bio/dynamics Project No. 80-2456)." Sielken, Inc.

VI. ADDITIONAL TESTING

Throughout this document and its attachments, Cheminova identifies additional testing it has planned or are ongoing. This testing is described below.

Cheminova is conducting two new toxicology studies to definitively resolve issues that have arisen in the methyl parathion hazard assessment. These two toxicology studies are as follows.

An acute dietary toxicity study in rats (neuropathology included). Cheminova will provide EPA with estimated dates for submission during the 60-day comment period.

A short-term (5-day) dermal toxicity study in rats (neuropathology included). Cheminova will provide EPA with estimated dates for submission during the 60-day comment period.

Cheminova is conducting field trials for alfalfa, grass, cotton, cotton gin byproducts, and for wheat AGF and anticipates submitting these studies by April 14, 1999.

Cheminova is conducting a sunflower processing study and anticipates submitting these data by April 14, 1999.

Cheminova intends to conduct the required ruminant and poultry feeding studies. In response to the 1997 DCI, Cheminova submitted a protocol for these studies to EPA on October 27, 1997; however, changes to the study designs proposed in the draft HED Chapter require revisions to the protocol before the studies can be conducted. Because of these important design issues, which are discussed in detail in Attachments D and E, these studies will be conducted in 1999.

VII. SUPPORTED USE PATTERNS FOR METHYL PARATHION

Based on its review of the issues raised in the draft HED chapter, Cheminova believes EPA's information on how methyl parathion is used in the United States contains some errors and confusion. Cheminova identifies below the uses, use patterns, and formulations for methyl parathion that will be supported for reregistration so that the Agency can conduct more appropriate risk assessments.

A. DECEMBER 1996 AGREEMENT WITH EPA

In December 1996, Cheminova and other "active" EC registrants (i.e., those formulators of EC end-use products with whom Cheminova had supply agreements) signed an agreement ("the December 1996 Agreement") with EPA designed to reduce the chance of illegal misuse of methyl parathion products. Generally, this Agreement required:

- cancellation of certain end-use registrations;
- formulations to contain less than 5.0 lbs of methyl parathion per gallon;
- packaging of all EC formulations in returnable-refillable containers with a tamper-resistant mechanism that does not permit removal of material without specialized equipment; and
- the inclusion of a stenching agent in all EC formulations.

The December 1996 Agreement did not apply to Mcap formulations or to products containing other active ingredients in addition to methyl parathion.

Cheminova has complied with all requirements of the December 1996 Agreement. However, for reasons discussed later in this section, Cheminova believes that some

product registrations that are no longer allowed pursuant to the Agreement are listed as active registrations by EPA.

B. METHYL PARATHION REGISTRATIONS

Cheminova believes that it is one of only two sources of technical methyl parathion registered in the United States. Although Cheminova believes that the technical methyl parathion sold by Griffin from an alternative source, its registration is based on citations of Cheminova's data. Because Griffin is relying on the citation of Cheminova's data to support its technical registration, Cheminova believes Cheminova's own decisions regarding supported uses of methyl parathion should be regarded as applicable to all other registrations unless other registrants are willing to develop their own data to support their registrations.

1. Technical Registrations

EPA states that Cheminova and Elf Atochem are the basic producers of methyl parathion in the United States. This statement is incorrect. Elf Atochem is not a basic producer of methyl parathion, it is a formulator. However, EPA recently granted a registration of a second source of technical methyl parathion to Griffin (Griffin Methyl Parathion Technical [EPA Reg. No. 1812-399]).

2. Registered Formulation Types

EPA has stated that methyl parathion may be formulated into EC, Mcap, and granular formulations. A search of the NPIRS database identifies active registrations for EC, Mcap, and granular formulations. However, Cheminova is supporting only the EC and Mcap formulations of methyl parathion. Cheminova urges the Agency to seek cancellation of all other formulation types that may be currently registered.

3. Registered End-Use Products

According to NPIRS, there are 15 active registrations of EC formulations, one active registration of an Mcap formulation, and one active registration of a granular formulation. In addition, there are nine active registrations of formulation mixtures.

Cheminova currently has one active registration of an EC formulation containing 4.0 lbs of methyl parathion per gallon and one EC formulation that is a mixture of ethyl parathion and methyl parathion. Elf Atochem has only one active registration of an Mcap formulation containing 2.0 lbs of methyl parathion per gallon.

Manufacturing-use products complying with the December 1996 Agreement prohibit the manufacture of any EC formulations containing more than 5.0 lbs of active ingredient per gallon. Moreover, the December 1996 Agreement provided for the cancellation of all end-use EC registrations held by signatory registrants that contain more than 5.0 lbs of methyl parathion per gallon. Accordingly, Cheminova believes that such registrations have either been canceled, or are effectively canceled, because such a product no longer can legally be manufactured. Therefore, Cheminova believes that these formulations should not have been included in any of the Agency's risk assessments.

Similarly, Cheminova believes that the granular product should be excluded from review because Cheminova is not supporting this formulation type for reregistration.

4. FIFRA Section 24(c) Registrations

NPIRS lists a total of 17 methyl parathion registrations under section 24(c) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). These 17 registrations have been issued by Alabama, California, Idaho, Indiana (2), Louisiana, Minnesota, Mississippi, Missouri, Nevada, Oregon, Texas (2), Washington (3), and Wisconsin. Cheminova and Elf Atochem are supporting only the section 24(c) registrations that are covered by the food/feed use patterns that will be supported through reregistration; only these registrations and registrations supported by others (e.g., IR-4) should be considered in the Agency's risk assessments. Cheminova recommends that the Agency determine whether any of the unsupported registrations are still active at the state level and whether maintenance fees have been paid by the registrants.

C. DIRECTIONS FOR USE

Methyl parathion is an insecticide-acaricide used on agricultural crops to control a variety of insect pests. There are no supported nonagricultural, residential, or domestic uses of methyl parathion.

1. Timing of Application

Because of its relatively short residual life, methyl parathion is often applied on an as-needed basis for the control of pests. It is generally applied after the first signs of pest damage.

2. Application Methods

EPA states that methyl parathion may be applied aerially and by airblast sprayer, chemigation, groundboom, and tractor-drawn granular spreaders. Each of these application techniques is discussed below.

a. Aerial application: Cheminova is supporting aerial applications of the methyl parathion EC formulation. With the exception of the use on grass and cotton, Cheminova agrees to amend its labels to require that all aerial applications of the EC formulation be made in a minimum of 2 gallons of water. Elf Atochem has stated that it will continue to support the aerial applications of its Mcap formulation with less than 2 gallons of finished sprays. Specifically, the Mcap label allows for 1 gallon of finished product per acre in corn. Elf Atochem has informed Cheminova that a minimum spray volume of 10 gallons per acre for aerial application to orchards is acceptable.

b. Airblast sprayer application: This is the principal application technique used to apply the Mcap formulation to orchards and groves. This technique is not applicable to the EC formulation because the EC formulation is not used on orchard or grove crops. Cheminova will continue to support this application method for the Mcap formulation only.

c. Chemigation: Cheminova is not supporting the application of the EC formulation through any type of irrigation system and has included language on its end-use label specifically prohibiting this application method. Chemigation is currently allowed only for the Mcap formulation.

d. Ground boom application: Cheminova will continue to support this application method.

e. Tractor-drawn granular spreader application: Cheminova is supporting granular formulations; therefore, application techniques for this formulation are not applicable to methyl parathion and should not have been included in the Agency's risk assessments.

3. Supported Food/Feed Uses and Use Patterns

Methyl parathion is a broad spectrum insecticide applied as a foliar spray to a variety of agricultural crops including fruits, vegetables, and grains. Methyl parathion has no registered domestic, residential, or indoor uses.

Cheminova believes that clarification of the uses and use patterns that it or others will support in the reregistration process will eliminate many of the concerns expressed by the Agency in its preliminary risk assessments (e.g., by eliminating problematic uses or use patterns). Tables 1 and 2, respectively, list the crops supported by Cheminova and Elf Atochem for the EC and Mcap formulations.

Methyl parathion application rates typically range from 0.25 lb a.i. per acre to 3.0 lbs a.i. per acre, depending on the target pest, season of application, and the level of infestation. For leafy vegetables, small grains, and other vegetable applications, methyl parathion is typically applied at rates from 0.25 lb a.i. per acre to 1.0 lb a.i. per acre. Recommended label rates for the Mcap formulation range from 0.125 lb a.i. per acre to 3.0 lbs a.i. per acre. The labeled maximum use patterns for EC and Mcap formulations for the supported crops are summarized in Tables 3 and 4, respectively. The typical use patterns for the supported crops for the EC and Mcap formulations are summarized in Tables 5 and 6.

Table 1. Methyl Parathion: Supported Food/Feed Uses for EC Formulations.

Root and Tuber Vegetables	**Legume Vegetables**
Carrots	Beans, succulent
Potatoes	Beans, dried
Sugar beets	Lima beans
Turnips	Peas, succulent
	Peas, dried
Bulb Vegetables	Soybeans
Onions	
	Fruiting Vegetables
Leafy Vegetables	Peppers[1]
Celery	
Lettuce (head and leaf)	**Miscellaneous Crops**
Spinach	Artichokes (globe)
	Cotton
Brassica Leafy Vegetables	Hops[1]
Broccoli	Rapeseed (canola)
Brussels sprouts	Sunflowers
Cabbage	
Cauliflower	**Cereal Grains** [2]
Collards	Barley
Kale	Corn, field
Mustard greens	Corn, sweet
	Oats
Cucurbit Vegetables	Rice
Melons[1]	Rye
	Wheat
Non grass Animal Feeds	
Alfalfa[3]	**Grass forage, fodder, and hay**
	Grasses

Notes:

1. This is a new use supported by IR-4. Cheminova does not intend to submit data to support this use.

2. Cheminova will support a cereal grain crop group tolerance excluding sorghum. Cheminova will not support the use of methyl parathion on sorghum.

3. Cheminova will not support the use for alfalfa grown for seed.

Table 2. Methyl Parathion: Supported Food/Feed Uses for the Mcap Formulation.

Root and Tuber Vegetables	**Pome Fruits**
Potatoes	Apples
Sweet potatoes*	Pears
Bulb Vegetables	**Fruiting Vegetables**
Onions	Tomatoes
Stone Fruits	**Tree Nuts**
Cherries	Almonds
Nectarines	Pecans
Peaches	Walnuts
Plums/prunes	
Legume Vegetables	**Cereal Grains**
Beans, dried	Wheat
Beans, succulent	Oats
Lentils	Barley
Peas	Corn (field and sweet)
Soybeans	Rice
	Rye
Miscellaneous Crops	
Cotton	
Grapes	
Peanuts	

*This is a 24(c) registration only.

Table 3. Methyl Parathion: Maximum Supported Use Patterns for EC Formulations.

Crop	Maximum Single Application Rate (1bs a.i./A)	Maximum Number of Applications per Year	Maximum Amount Applied per Year (lbs a.i./A) [a]	Minimum Application Interval (days)	Minimum Pre-harvest Interval (days)
Root and Tuber Vegetables					
Carrots	1.0	6	6.0	7	15
Potatoes	1.5	6	9.0	7	5
Sugar beets	0.375	6	2.25	7	20
Turnips	0.75	2	1.5	7	7
Bulb Vegetables					
Onions	1.0	6	6.0	7	15
Leafy Vegetables					
Celery	1.0	2	2.0	14	15
Lettuce (head and leaf)	1.0	6	6.0	7	15
Spinach	1.0	6	6.0	7	15
Brassica Leafy Vegetables					
Broccoli	1.5	6	7.0	7	7
Brussels sprouts [b]	1.5	6	7.0	7	7
Cabbage	1.5	6	8.0	7	10-21 [c]
Cauliflower [b]	1.5	7	7.0	7	7
Collards [d]	1.5	6	8.0	7	10-21 [c]
Kale	1.5	6	8.0	7	10-21 [c]
Mustard greens	1.5	6	8.0	7	10-21 [c]
Legume Vegetables					
Beans, succulent	1.5	6	9.0	7	15
Beans, dried	1.5	6	9.0	7	15
Lima beans	1.5	6	9.0	7	21
Peas, succulent	1.0	6	6.0	7	10-15 [e]
Peas, dried	1.0	6	6.0	7	10-15 [e]
Soybeans [f]	0.5	2	1.0	5	20
Cucurbit Vegetables					
Melons [g]	0.5	5	2.5	7	7

Fruiting Vegetables					
Peppers [g]	1.0	5	5.0	7	15

Table 3. Methyl Parathion: Maximum Supported Use Patterns for EC Formulations *(continued)*.

Crop	Maximum Single Application Rate (lbs a.i./A)	Maximum Number of Applications per Year	Maximum Amount Applied per Year (lbs a.i./A) [1]	Minimum Application Interval (days)	Minimum Pre-harvest Interval (days)
Cereal Grains [h]					
Barley [i]	1.25	6	6.5	7	15
Corn, field	1.0	6	6.0	7	12
Corn, sweet	0.5	6	3.0	3	3
Oats [i]	1.25	6	6.5	7	15
Rice	0.75	6	4.5	7	15
Rye [i]	1.25	6	6.5	7	15
Wheat	1.25	6	6.5	7	15
Miscellaneous Crops					
Artichokes (globe)	1.0	4	4.0	7	7
Cotton	3.0	10	26.0	3	7
Hops [g]	1.0	3	3.0	7	15
Rapeseed (canola)	1.0	4	3.0	7	28
Sunflowers	1.0	3	3.0	7	30

a The maximum amounts of methyl parathion allowed to be applied per season reported in this table are based on the maximum amount applied during the conduct of Cheminova's magnitude of the residue field trials; these amounts are <u>not</u> the result of multiplying the maximum single application rate and the maximum number of applications made. In Cheminova's field trials, multiple applications were applied at various rates up to the maximum amounts reported in this table.

b No data have been submitted to support this use. According to the November 24, 1992, Methyl Parathion Residue Chemistry Registration Standard Update, data can be translated from broccoli to support this use. The use pattern specified in this table is based on the use pattern for broccoli.

c The preharvest interval of 10 days applies if the final application is less than 1.0 lb a.i./acre. A 21-day preharvest interval applies if the final application is 1.0 lb a.i./acre or more.

d No data have been submitted to support this use. According to the November 24, 1992, Methyl Parathion Residue Chemistry Registration Standard Update, data can be translated from mustard greens to support this use. The use pattern specified in this table is based on the use pattern for mustard greens.

e The preharvest interval of 10 days applies if the final application is less than 1.0 lb a.i./acre. A 15-day preharvest interval applies if the final application is 1.0 lb a.i./acre or more.

f Cheminova is supporting the use of the EC formulation of methyl parathion on this crop; however, Cheminova will not support the use on forage and hay. Cheminova plans to add a feeding/grazing restriction to its end-use labels to prohibit use on forage and hay.

g This is a new use supported by IR-4. Cheminova does not intend to submit any data to support this use. The use pattern reported here is the use pattern proposed by IR-4.

h Cheminova will support a cereal grain crop group tolerance, but it will not support the use of the methyl parathion EC formulations on sorghum.

i Cheminova is supporting the use of the EC formulation of methyl parathion on barley, oats, and rye. Wheat data were translated to support these uses. The use patterns stated in this table for these crops are the same as that tested for wheat.

Table 4. Methyl Parathion: Maximum Supported Use Patterns for the Mcap Formulation.

Crop	Maximum Single Application Rate (lbs a.i./A)	Maximum Number of Applications per Year	Maximum Amount Applied per Year (lbs a.i./A)	Minimum Application Interval (days)	Minimum Pre-harvest Interval (days)
Root and Tuber Vegetables					
Potatoes	0.5	6	9.0	7	5
Sweet potatoes	0.75	8	6.0	7	5
Bulb Vegetables					
Onions	1.0	6	6.0	7	15
Legume Vegetables					
Beans, dried	1.0	6	6	3	15
Beans, succulent	1.0	6	6	7	7
Lentils	0.5	3	1.5	11	14
Peas	0.5	2	1.0	7	15
Soybean	1.0	2	2.0	7	30
Pome Fruits					
Apples	2.0	5	9.0	7	21
Pears	2.0	5	9.0	7	21
Stone Fruits					
Cherries	1.5	6	9.0	7	15
Nectarines	2.0	6	12.0	7	30
Peaches	2.0	6	12.0	7	30
Plums/prunes	1.5	4	6.0	7	15
Fruiting Vegetables					
Tomatoes	1.0	5	5.0	6	15
Tree Nuts					
Almonds	2.0	6	12.0	21	24
Pecans	2.0	8	16.0	13	15
Walnuts	2.0	4	8.0	21	14
Cereal Grains					
Barley	0.75	3	2.25	7	14
Corn (field and sweet)	1.0	5	5.0	14	12
Oats	0.75	3	2.25	7	14

Rice	0.75	6	4.5	21	15
Rye	0.75	3	2.25	7	14
Wheat	0.75	3	2.25	7	14
Miscellaneous Crops					
Cotton	1.0	8	8.0	5	14
Grapes	1.0	2	2.0	7	28
Peanuts	1.0	4	4.0	14	15

Table 5. Methyl Parathion: Typical Use Patterns for EC Formulations.

Crop	Typical Single Application Rate (lbs a.i./A)	Typical Number of Applications per Year	Typical Amount Applied per Year (lbs a.i./A) [a]	Typical Application Interval (days)	Typical Pre-harvest Interval (days)
Root and Tuber Vegetables					
Carrots	1.0	2	2.0	7-10	15
Potatoes	1.5	3	4.5	7-10	6
Sugar beets	0.5	2	1.0	7-10	20
Turnips	0.75	2	1.5	7-10	10
Bulb Vegetables					
Onions	0.5	2	1.0	7-10	15
Leafy Vegetables					
Celery	1.0	2	2.0	10-14	15
Lettuce	1.0	1	1.0	7	15
Spinach	1.0	2	2.0	7-10	15
Brassica Leafy Vegetables					
Broccoli	1.5	2	3.0	7-10	7
Brussels sprouts [b]	1.5	2	3.0	7-10	7
Cabbage	1.5	2	3.0	7-10	10-21 [c]
Cauliflower [b]	1.5	2	3.0	7-10	7
Collards [d]	1.5	2	3.0	7-10	10-21 [c]
Kale	1.5	2	3.0	7-10	10-21 [c]
Mustard greens	1.5	2	3.0	7-10	10-21 [c]
Legume Vegetables					
Beans, succulent	1.5	2	3.0	7-10	15
Beans, dried	1.5	2	3.0	7-10	15
Peas, succulent	1.0	3	3.0	7-10	10-21 [e]
Peas, dried	1.0	3	3.0	7-10	10-21 [e]
Lima beans	1.5	2	3.0	7-10	15
Soybeans [f]	0.5	2	1.0	5-7	20
Cereal Grains [g]					
Barley [h]	0.75	2	1.5	7-10	15
Corn, field	0.5	2	1.0	5-7	12
Corn, sweet	0.5	2	1.0	5-7	12

Oats [h]	0.75	2	1.5	7-10	15
Rice	0.75	2	1.5	7-10	15
Rye [h]	0.75	2	1.5	7-10	15
Wheat	0.75	2	1.5	7-10	15
Cucurbit Vegetables					
Melons [i]	0.5	5	2.5	7	7

Table 5. Methyl Parathion Typical Use Patterns for EC Formulations *(continued)*.

Crop	Typical Single Application Rate (lbs a.i./A)	Typical Number of Applications per Year	Typical Amount Applied per Year (lbs a.i./A) [1]	Typical Application Interval (days)	Typical Pre-harvest Interval (days)
Fruiting Vegetables					
Peppers [i]	1.0	5	5.0	7	15
Miscellaneous Crops					
Artichokes (globe)	1.0	4	4.0	7	7
Cotton [j]	2.0	3	6.0	7	7
Hops [k]	1.0	3	3.0	7	28
Rapeseed (canola)	0.5	2	1.0	7	28
Sunflowers	1.0	2	2.0	3-5	30

a. The maximum amount of methyl parathion allowed to be applied per season was calculated by multiplying the typical single application rate by the typical number of applications made per season.

b. No data have been submitted to support this use. According to the November 24, 1992, Methyl Parathion Residue Chemistry Registration Standard Update, data can be translated from broccoli to support this use. The use pattern specified in this table is based on the use pattern for broccoli.

c. The preharvest interval of 10 days applies if the final application is less than 1.0 lb a.i./acre. A 21-day minimum preharvest interval applies if the final application is 1.0 lb a.i./acre or more.

d. No data have been submitted to support this use. According to the November 24, 1992, Methyl Parathion Residue Chemistry Registration Standard Update, data can be translated from mustard greens to support this use. The use pattern specified in this table is based on the use pattern for mustard greens.

e. The preharvest interval of 10 days applies if the final application is less than 1.0 lb a.i./acre. A 15-day minimum preharvest interval applies if the final application is 1.0 lb a.i./acre or more. Typically, peas are harvested as much as 21 days after the last application.

f. Cheminova is supporting the use of the EC formulation of methyl parathion on this crop; however, it will not support the use on forage and hay. Cheminova plans to add a feeding/grazing restriction to its end-use labels to exclude use on forage and hay.

g. Cheminova will support a cereal grain crop group tolerance, but it will not support the use of the methyl parathion EC formulations on sorghum.

h. Cheminova is supporting the use of the EC formulation of methyl parathion on barley, oats, and rye. In the 90-day response to the April 10, 1997, data call-in notice for methyl parathion, Cheminova requested that EPA translate data submitted for wheat to support the use of the methyl parathion EC formulation on these crops.

i. This is a new use supported by IR-4. Cheminova does not intend to submit any data to support this use. The use patterns reported here is the use pattern proposed by IR-4.

j. The typical application rates for cotton are directly related to the target pest present during a particular growing season. In most years, methyl parathion will only be used against one or two of these pests. See Table 9 for clarification of use patterns for each target pest.

Table 6. Methyl Parathion: Typical Use Patterns for the Mcap Formulation.

Crop	Typical Single Application Rate (lb a.i./A)	Typical Number of Applications Per Year	Typical Maximum Amount Applied Per Year	Typical Application Interval (days)	Typical Pre-Harvest Interval (days)
Root and Tuber Vegetables					
Potatoes	0.375	1	0.375	NA*	15
Sweet potatoes	0.375	1	0.375	NA	15
Bulb Vegetables					
Onions	0.375	1	0.375	NA	15
Legume Vegetables					
Beans, dry	0.25	6	1.5	5	15
Beans, succulent	0.25	2	0.5	7	3
Lentils	0.5	3	1.5	11	14
Peas	0.375	1	0.375	NA	15
Soybeans	0.25	1	0.25	NA	30
Pome Fruits					
Apples	0.625	2	1.25	7	21
Pears	0.625	1	0.625	NA	28
Stone Fruits					
Cherries	0.375	2	0.75	7	14
Nectarines	0.5	1	0.5	NA	28
Peaches	0.375	2	0.75	7	21
Plums/prunes	0.435	2	0.87	7	28
Fruiting Vegetables					
Tomatoes	0.25	1	0.25	NA	15
Tree Nuts					
Almonds	2.0	6	12.0	21	14
Pecans	0.435	2	0.87	21	51
Walnuts	0.875	1	0.875	NA	30
Cereal Grains					
Barley	0.375	1	0.375	NA	21
Corn	0.25	2	0.5	14	30
Oats	0.375	1	0.375	NA	21
Rice	0.375	1	0.375	NA	21

Rye	0.375	1	0.375	NA	21
Wheat	0.375	1	0.375	NA	21
Miscellaneous Crops					
Cotton	0.125	5	0.625	3	7
Grapes	2.5	3	7.5	7	60
Peanuts	1.0	4	4.0	14	15

*NA = not applicable because there is only one application.

4. Supported Non-Food/Feed Uses and Use Patterns

Cheminova's current technical label allows the use of methyl parathion for the following terrestrial, nondomestic, nonfood uses:

- jojoba (special local need);
- guayule (special local need);
- field grown ornamental flowering plants;
- chrysanthemums;
- daisies;
- marigolds;
- nursery stock;
- nonagricultural lands; and
- wastelands.

Although these uses are currently allowed by Cheminova's technical label, Cheminova will not continue to support these uses. These uses are not included on Cheminova's end-use labels.

Cheminova also is not supporting the use of methyl parathion for these purposes:

- to control pests in and around nurseries and nursery plantings;
- for public health control (mosquitoes and rodents);
- for regulatory pest control (government-led control of infestations or for quarantine purposes);
- for landscape maintenance;
- on Christmas tree plantations; or
- on pine forests.

Cheminova urges the Agency to cancel any existing registrations of such uses.

D. METHYL PARATHION LABELS

As the primary registrant that has submitted most of the data to support methyl parathion registrations, Cheminova agrees with HED's recommendation (page 5 of the June 11, 1998, draft Residue Chemistry Science Chapter) that the end-use product data call-in notices for methyl parathion must require that all registrants amend their end-use product labels to make them consistent with the basic producer label. Cheminova is willing to assume a leadership role in working with EPA and the end-use registrants to make these revisions.

E. USE OF METHYL PARATHION IN THE UNITED STATES

According to a survey conducted by the National Center for Food and Agricultural Policy, approximately 97% of the methyl parathion sold in the United States is used on 11 crops. A summary of these uses is presented in Table 7 and Figure 1 below.

Table 7. U.S. EPA Estimates of the Amount of Methyl Parathion Used in the United States from a Survey Conducted by the National Center for Food and Agricultural Policy for 1991-1993 and 1995.

Ranking	Crop	Total Amount Used Per Year (lbs a.i./crop/year)	Percent of the Total Amount Used on This Crop Each Year (%)
1	Cotton	3,396,754	57.0
2	Field corn	770,991	13.0
3	Alfalfa	418,692	7.0
3	Wheat	308,430	5.2
4	Sunflowers	217,221	3.7
5	Apples	177,141	3.0
7	Rice	149,555	2.5
8	Soybeans	115,659	2.0
9	Peaches	93,511	1.6
10	Potatoes	70,505	1.2
11	Sweet corn	59,912	1.0
Subtotal of Top 11 Uses		5,778,371	97.2
Subtotal for All Other Uses		183,369	2.8
Grand Total		**5,961,740**	**100.0**

Since 1994, the reduction of use of methyl parathion has been a clear trend. A number of factors are related to this decrease, including the elimination of the major cotton pests by the Boll Weevil Eradication Programs, the decreased dependence on chemicals as a sole means of controlling agricultural pests (i.e., use of integrated pest management programs), and the growing popularity of crops engineered to produce natural toxins as a defense against target pests (i.e., *bacillus thurengiensis* in cotton). In addition, the recall and packaging requirements of the December 1996 Agreement with EPA has resulted in a major reduction in sales of the EC formulations (see Table 8).

Figure 1. Methyl Parathion Food/Feed Crops

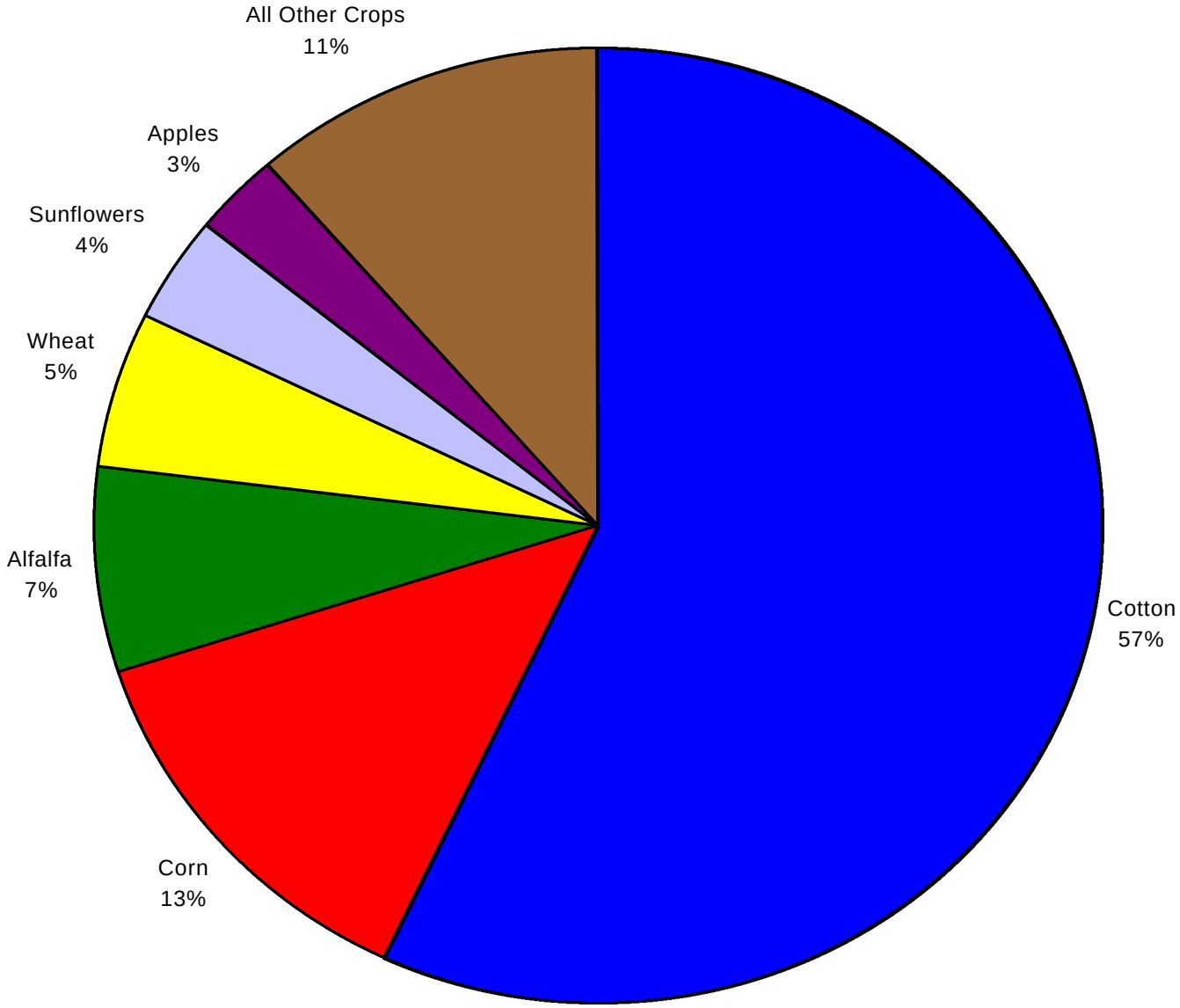

Table 8. Effect of the Recall and Packaging Restrictions on Sales of Methyl Parathion EC Products after the December 1996 Agreement with EPA.

Cross Reference Number 1 This cross reference number noted as a place-holder on this page and is used in place of the following whole page at the indicated volume and page reference.

This deleted page is in CONFIDENTIAL ATTACHMENT H.

Approximately 85% to 90% of the methyl parathion EC formulation sold in the United States is used on cotton. The typical application rates for cotton are directly related to the target pest present during a particular growing season (see Table 9). In most years, methyl parathion will only be used against one or two pests.

Historically, the typical application on cotton has been to control the boll weevil, but as boll weevil eradication efforts have progressed, the use of methyl parathion has decreased significantly.

Table 9. Typical Use Patterns for the Methyl Parathion EC Formulation on Cotton.

Pest	Typical Application Rates (lbs a.i./acre)	Typical Number of Applications per Year	Typical Amount Applied per Year (lbs a.i./acre)
Boll weevil	0.5	6	3.0
Thrips	0.33	3	0.99
Cotton leafworms Cotton leaf perforator Cutworms False cinch bugs	1.0	3	3.0
Grasshoppers Armyworms	3.0	2	6.0
Aphids	0.5	4	2.0
Stink bugs	2.0	3	6.0
Bollworms	2.0	3	6.0

VIII. Cheminova's Comments on EPA's Memorandum titled "Methyl Parathion. The HED Chapter of the Reregistration Eligibility Decision Document (RED)" (Diana Locke, September 1, 1998) and Its Attachments

Cheminova's comments on EPA's September 1, 1998, memorandum are presented below. Detailed comments on each of the attachments to the memorandum appear as separate attachments to this document.

A. HAZARD CHARACTERIZATION

1. Hazard Profile

EPA states that the methyl parathion database is complete except for a developmental neurotoxicity study. Cheminova believes that this study is unnecessary and that EPA has based the requirement on inappropriate criteria and inappropriate use of flawed studies from the scientific literature. Cheminova's position is elaborated in Attachment A.

Cheminova disagrees with EPA's interpretation and use of many of the studies in the methyl parathion database. Detailed study reviews appear in Attachments A and C.

2. Endpoint Selection

Cheminova has reassessed the results of the core developmental, subchronic, and chronic studies using the JMPR/WHO criteria for determining the adversity of cholinesterase-related findings agreed on in September 1998. In general, the JMPR/WHO approach calls for use of the following as regulatory endpoints: clinical signs of cholinesterase (ChE) inhibition; statistically significant brain ChE inhibition; or statistically significant red blood cell (RBC) ChE inhibition that is more than 20% decreased compared to control.

It should be noted that some of the endpoints for risk assessment proposed by Cheminova are preliminary, pending completion of ongoing toxicological studies.

a. Chronic Dietary and Occupational Risk Assessments

The study and endpoint selection proposed by EPA for selecting a reference dose and for chronic dietary and occupational risk assessments is inappropriate, for the following reasons:

- EPA considered only the Daly and Hogan, 1982, chronic (2-year) rat study. This study has some limitations, which preclude relying on it alone for developing an RfD, including the fact that the number of animals evaluated for neuropathological findings is not adequate to define a NOEL for peripheral nerve effects, and the fact that the high incidence of intercurrent infection in this study may have compromised the chronic toxicity evaluation.

- Cheminova does not agree with the NOEL of 0.02 mg/kg bw/day determined by EPA from this study. Cheminova believes that 0.2 mg/kg bw/day is a no-observed adverse-effect level (NOAEL) dose in this study, based on the absence of treatment-related effects on brain or RBC cholinesterase, clinical signs, clinically significant changes in hematological parameters, or treatment-related neuropathological findings.

- EPA memoranda reviewing the chronic rat studies have repeatedly discussed the need for a peer review for characterization of the NOEL for methyl parathion neurotoxicity (specifically for neuropathology). Cheminova agrees this would be appropriate, both because of the limitations of the 2-year study discussed above, and particularly because a reevaluation of nervous system tissues from the 12-month chronic rat study (Brennecke, 1996) that had been requested by EPA to help elucidate this issue showed no treatment-related peripheral nerve lesions at any dose. Cheminova would like to discuss with the Agency whether and how such a peer review evaluation could be conducted.

In the interim, Cheminova believes 0.11 mg/kg bw/day is a reasonable NOAEL for use in deriving a chronic RfD, based on findings in all three of the longer term rat studies (the 1- and 2-year chronic studies and the rat subchronic neurotoxicity study) that included neuropathological evaluations. Good concordance is shown for the results of these studies for most of the parameters evaluated, and the NOEL of 0.11 mg/kg bw/day from the 1-year rat study is a conservative choice for an NOAEL for chronic toxicity.

The conservatism of this choice for evaluation of the risks from intermediate to longer term exposures to methyl parathion is also supported by a human

30-day oral study of methyl parathion, which showed an NOEL of 0.31 mg/kg bw/day for RBC cholinesterase inhibition (Rider et al., 1971). Although Cheminova believes that the available data from this study are too limited to be used exclusively as a basis for risk assessment, the human study results provide assurance that the animal study results are not underpredicting toxicity to humans.

b. Acute Dietary and Short-Term Occupational Risk Assessments

EPA is proposing to use the NOEL from the acute neurotoxicity study. This is overly conservative for the following reasons:

- The low dose used in the study was some 300 times lower than the mid dose. Cheminova's objective in the acute neurotoxicity study was to characterize neurotoxic potential at high doses, rather than to determine a NOEL. Moreover, the acute neurotoxicity study is a gavage study providing a bolus dose of test material, which does not correlate well to toxicity data obtained by a dietary route. The dietary subchronic data predict that if dietary administration were used, an acute NOEL could conservatively be found at a much higher dose level than the acute gavage study NOEL.

- For short-term occupational exposure, the primary route of exposure would most likely be dermal, with a relatively slower rate of systemic absorption compared to that in a bolus gavage study. The dietary route of the subchronic neurotoxicity study results in a slower absorption of test material that is more comparable to occupational exposure than a bolus gavage dose. The repeated exposure scenario in the subchronic study also provides a conservative assessment of the effects of short-term exposures.

Cheminova is conducting a new oral acute study, using dietary administration and a larger number of dose levels, to better characterize the acute dietary NOEL for methyl parathion in the rat. Cheminova is also conducting a new short-term dermal study in rats. Both studies will include neuropathological evaluations.

Until the new studies are available, Cheminova suggests that, of the available methyl parathion toxicity data, using the NOEL of 0.3 mg/kg/day, extrapolated from the dietary subchronic neurotoxicity study, is the most appropriate choice for hazard evaluation of both the acute (dietary) and short-term (occupational) exposure scenarios.

c. Intermediate-Term Occupational Risk Assessment

EPA is proposing to use the chronic 2-year study of methyl parathion as the basis for intermediate-term occupational risk assessment. This is inappropriate for the following reasons:

- The subchronic neurotoxicity study provides a more realistic exposure scenario for estimation of risks potentially associated with intermediate-term exposure than does the rat chronic study. The subchronic study characterized neurotoxicity, including results of detailed functional observational battery, motor activity, and neuropathological evaluations. The time frame of this study also more closely approximates that of an intermediate-term exposure study.

d. Inhalation Risk Assessment

EPA is proposing to use the chronic 2-year study of methyl parathion as the basis for risk assessment from any inhalation exposure. Cheminova disagrees with EPA's approach, for the following reasons:

- First, it is not appropriate to select an NOEL from a chronic study as the basis for risk assessment for acute and intermediate exposures as well as for long-term exposures. Endpoints from studies of the appropriate duration should be selected for each different exposure scenario.

- Second, both occupational and ambient exposures to methyl parathion may be reasonably expected to be seasonal, with occasional acute peaks, rather than chronic.

Cheminova suggests that either the 3-month neurotoxicity study (NOEL of 0.1 mg/kg bw/day) or the 1-year chronic rat study (NOEL of 0.11 mg/kg bw/day) would provide more appropriate choices for risk assessment (depending on the duration of the exposure in question).

e. Dermal Exposure Risk Assessment

For dermal absorption, EPA is proposing to apply a 100% adsorption factor to any dermal exposure because the Agency lacks confidence in a much lower dermal absorption value predicted based on a 28-day rabbit dermal toxicity study. This is unduly conservative. Other *in vitro* data and rat *in vivo* data are available which estimate dermal absorption of the technical or formulated product to be in the 10% to 25% range of that from oral exposures. As noted above, Cheminova is currently developing additional dermal data, which should definitively resolve this issue.

3. Safety Factors

EPA's decision to retain the FQPA additional 10X safety factor for infants and children in dietary risk assessments appears to be based on two different types of findings:

- increased pup susceptibility to methyl parathion compared to adults; and
- neuropathology seen "at [a] low dose level" in the acute neurotoxicity test of methyl parathion.

For the reasons developed below and in Attachment A, Cheminova does not believe that this additional 10X safety factor is appropriate for methyl parathion.

Cheminova concurs with EPA's position in the cover letter to the attachments to the HED document that the additional 10X safety factor is inappropriate for occupational risk assessments. However, EPA needs to correct the documents in the package so that they reflect this position. Since there are no residential uses for methyl parathion being supported for reregistration, there is no need to develop a reference dose for this exposure scenario.

Developmental and Reproductive Study Findings

The existing developmental and reproductive toxicity data on methyl parathion do not call for the use of an extra 10-fold safety factor. They also do not provide a substantive basis for selectively requiring a developmental neurotoxicity study on methyl parathion at a time when the test is not being required for other similar pesticides for the following reasons:

- Guideline-quality developmental toxicity studies in rats and rabbits show no evidence of unique fetal susceptibility to methyl parathion after *in utero* exposure.

- A Guideline-quality, two-generation rat reproductive toxicity study revealed no evidence of increased susceptibility of offspring to methyl parathion.

- A study of poor quality on the effects of *in utero* exposure to methyl parathion, a summary of which was published in the public literature, does not show developmental effects or indicate an increased susceptibility of the pups compared to the adults in the study. Some behavioral changes in offspring were seen from the lower dose; however, no similar changes occurred in high-dose animals. Further, the behavioral findings were not consistent with the dose-related ChE inhibition, raising serious questions about the treatment-relationship of the behavioral findings.

- Three studies summarized in journal articles on the effects of methyl parathion injected directly into pups at very high dose levels have little if any relevance to actual situations of potential human exposure. These studies use intraperitoneal or subcutaneous routes of administration that cannot be extrapolated to human exposure scenarios and that, in themselves, may be stressful to neonatal or young pups. EPA should heed its Scientific Advisory Panel's advice that, because young animals' detoxification enzyme levels may be lower than adult levels, high doses of ChE inhibitors (but *not* low levels) may overwhelm the young animals' defenses.

- EPA fails to critically evaluate the published literature cited by EPA as relevant to developmental or pup susceptibility to methyl parathion. Each of these studies from the published literature has one or more significant deficiencies in study design, data interpretation, and/or reporting. Moreover, the studies were not conducted in accordance with Good Laboratory Practices (GLP). Thus, these studies do not provide an adequate basis for retaining the additional safety factor.

In summary, the reliable Guideline developmental and reproductive toxicity studies demonstrate a lack of treatment-related effects except at high doses and also show no evidence of increased susceptibility to fetuses or pups. The questionable, non-Guideline, non-GLP studies either provide no reliable indication of adverse developmental effects (Gupta et. al., 1985) or were conducted using inappropriate routes of administration and show effects only at extremely high doses not relevant to the regulation of residues on food.

Further, the mere absence of a newly required developmental neurotoxicity study should not be used to support an additional safety factor in the absence of reliable existing data indicating a potential for developmental neurotoxicity, for

the reasons set forth in the Implementation Working Group's June 1998 issue paper "The FQPA Additional Safety Factor."

Neurotoxicity Study Findings

Neuropathological findings at high dose levels do not constitute a justifiable basis for imposing the extra 10-fold safety factor or for requiring a developmental neurotoxicity study for the following reasons:

- The acute neurotoxicity study results showed treatment-related neuropathological findings only at high and severely toxic (lethal or near-lethal) doses.

- Data from the subchronic dietary neurotoxicity study and the 12-month special eye and nerve study also provide support for the absence of adverse neuropathological effects at low dietary dose levels.

- The data on neuropathological effects do not indicate any unevaluated potential for developmental effects or other adverse effects in fetuses, infants, or children from the residue levels found on foods.

B. EXPOSURE CHARACTERIZATION

1. Occupational Exposure

EPA states that methyl parathion can be applied with aerial equipment, airblast sprayer, chemigation, and ground-boom sprayer. Cheminova is not supporting the application of methyl parathion EC formulations by chemigation and its end-use labels specifically prohibit this application technique. However, we understand that Elf Atochem is supporting this application technique for the Mcap formulation.

EPA estimated occupational exposure to methyl parathion using exposure values calculated using the Pesticide Handler Exposure Database (PHED Version 1.1) and protection factors that are applied to represent various risk mitigation options (i.e., the use of personal protection equipment (PPE)). Cheminova has several concerns about the Agency's approach and provides specific comments on these calculations in Attachment F. Cheminova's concerns are as follows:

- It is unclear from Table 2 and 3 of EPA's March 2, 1998, *Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Methyl Parathion* what the Agency specified as additional PPE (for example label-required head gear).

- It is unclear to Cheminova if the Agency applied a 50% reduction factor to the dermal exposure body section "head" of the PHED exposure estimate to reflect the label-required head gear.

Cheminova recalculated the methyl parathion intermediate-term surrogate postapplication exposure assessment for the Mcap formulation, using 25% dermal absorption and the NOEL of 0.1 mg/kg bw/day.

2. Residential Exposure

EPA claims that commercial applicators could potentially apply methyl parathion to fruit trees in residential settings and is requesting that the labels be amended to specifically prohibit such use. Cheminova notes that there are no legal residential uses for methyl parathion. In fact, Cheminova's technical label states that the technical material may be formulated only into formulations for use on "terrestrial, non-domestic food uses" and "terrestrial, non-domestic non-food uses." In addition, Cheminova's end-use label states that methyl parathion is "not for use in or around the home." Cheminova believes that any residential use would be a violation of language already on its labels and therefore would constitute an illegal misuse of the product. If there are labels held by other registrants that allow such a use, EPA should demand that these registrants amend their labels accordingly.

C. RISK ASSESSMENT/CHARACTERIZATION

1. Dietary Exposure

a. Supported Uses

EPA included in its risk assessments only those agricultural uses of methyl parathion that are being supported for reregistration. However, Cheminova notes that EPA erroneously included kohlrabi, which is not to be supported according to Cheminova's and Elf Atochem's responses to the April 10, 1997, DCI.

b. Chronic Dietary Risk

EPA conducted a preliminary (Tier I) chronic dietary risk assessment using reassessed tolerance levels and percentage crop treated data. This Tier I assessment yielded a chronic dietary risk estimate of > 11,000% of the chronic RfD. EPA stated in the executive summary that this estimate indicated unacceptable risk. However, EPA's own Guidance provides that a Tier I assessment is only a screening tool and that unacceptable results from a Tier I assessment do not show that risks are unacceptable, but rather imply the need to conduct higher-tier assessment employing more accurate exposure data.

Cheminova retained Novigen Sciences, Inc., to conduct a Tier II chronic dietary exposure assessment for methyl parathion. This more refined assessment shows that chronic dietary exposure is less than the RfD of 0.02 mg/kg/day when the appropriate 100X safety factor is used. The use-up of the RfD was 5.58% for the U.S. population and 16.7% for non-nursing infants, the most sensitive population. Tables 10 and 11 (below) summarize the input parameters and results for this chronic exposure assessment[1]. As discussed in Attachment A, Cheminova believes that the chronic RfD should be 0.11 mg/kg/day based on results from the rat subchronic and chronic studies. This higher RfD will further lower the estimated dietary risk. A detailed report describing this assessment (as modified to reflect the higher RfD) will be provided to the Agency during the public comment period.

[1] This assessment included all supported crops based on Cheminova's and Elf Atochem's responses to the April 10, 1997, methyl parathion DCI. Recently, Elf Atochem decided to support the use of the Penncap-M® formulation on sweet potatoes. Sweet potatoes were not included in the following assessment. Sweet potatoes will be added after Elf Atochem has completed the supporting potato residue study.

Table 10. Chronic Dietary Risk Analysis Performed by Cheminova

Results with Reference Dose = 0.0002

CNOVA Ver. 6.43
DEEM CHRONIC analysis for METHYL PARATHION (1994-96 data)
Residue file name: CHRONMP7.R96 Adjustment factor #2 used.
Analysis Date 10-22-1998 Residue file dated: 10-19-1998/10:30:45/1
Reference dose (RfD, CHRONIC) = 0.000200 mg/kg body-wt/day
COMMENT 1: Current RfD and NOEL

Total Exposure by Population Subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Total Exposure Percent of Rfd
U.S. Pop - 48 states - all seasons	0.000011	5.6%
U.S. Population - spring season	0.000011	5.6%
U.S. Population - summer season	0.000012	6.2%
U.S. Population - autumn season	0.000010	5.2%
U.S. Population - winter season	0.000011	5.3%
Northeast region	0.000011	5.6%
Midwest region	0.000011	5.4%
Southern region	0.000011	5.3%
Western region	0.000012	6.2%
Hispanics	0.000013	6.5%
Non-Hispanic whites	0.000011	5.3%
Non-Hispanic blacks	0.000011	5.7%
Non-Hispanic other than black or white	0.000015	7.6%
All infants (<1 year)	0.000030	14.9%
Nursing infants (<1 year)	0.000018	9.1%
Non-nursing infants (<1 year)	0.000034	16.8%
Children (1-6 years)	0.000026	13.0%
Children (7-12 years)	0.000015	7.3%
Females (13-19 yrs/not preg. or nursing)	0.000008	4.0%
Females (20+ years/not preg. or nursing)	0.000008	3.9%
Females (13-50 years)	0.000008	3.8%
Females (13+/pregnant/not nursing)	0.000009	4.7%
Females (13+/nursing)	0.000012	6.0%
Males (13-19 years)	0.000009	4.6%
Males (20+ years)	0.000010	4.8%
Seniors (55+)	0.000009	4.4%

Table 11. Inputs Used By Cheminova For Its Chronic Dietary Risk Assessment

Food Code	EPA Code	Crop Group	Food Name	Residue (ppm)	Adj. Factrs #1	Adj. Factrs #2
13	01014AA	O	Grapes	0.001637	1.00	1.00
14	01014DA	O	Grapes-raisins	0.001637	0.04	1.00
15	01014JA	O	Grapes-juice	0.001637	0.03	1.00
40	03001AA	14	Almonds	0.095000	1.00	0.01
47	03008AA	14	Pecans	0.050000	1.00	0.01
48	03009AA	14	Walnuts	0.050000	1.00	0.01
52	04001AA	11	Apples	0.001469	1.00	1.00
53	04001DA	11	Apples-dried	0.001469	5.00	1.00
54	04001JA	11	Apples-juice/cider	0.000473	1.00	1.00
56	04003AA	11	Pears	0.001086	1.00	1.00
57	04003DA	11	Pears-dried	0.001086	5.00	1.00
61	05002AA	12	Cherries	0.182000	1.00	0.11
62	05002DA	12	Cherries-dried	0.182000	4.00	0.11
63	05002JA	12	Cherries-juice	0.182000	1.50	0.11
64	05003AA	12	Nectarines	0.003312	1.00	1.00
65	05004AA	12	Peaches	0.015881	1.00	1.00
66	05004DA	12	Peaches-dried	0.015881	7.00	1.00
67	05005AA	12	Plums (damsons)	0.015278	1.00	1.00
68	05005DA	12	Plums-prunes (dried)	0.015278	5.00	1.00
69	05005JA	12	Plums/prune-juice	0.015278	1.40	1.00
125	08020AA	O	Hops	0.970000	1.00	0.49
155	11003AA	8	Peppers-sweet(garden)	0.000084	1.00	1.00
156	11003AB	8	Peppers-chilli incl jalapeno	0.000084	1.00	1.00
157	11003AD	8	Peppers-other	0.000084	1.00	1.00
158	11004AA	8	Pimientos	0.000084	1.00	1.00
159	11005AA	8	Tomatoes-whole	0.000042	1.00	1.00
160	11005JA	8	Tomatoes-juice	0.000042	0.05	1.00
161	11005RA	8	Tomatoes-puree	0.000042	0.11	1.00
162	11005TA	8	Tomatoes-paste	0.000042	0.11	1.00
163	11005UA	8	Tomatoes-catsup	0.000042	0.06	1.00
166	13002AA	4B	Celery	0.000220	1.00	1.00
168	13005AA	5A	Broccoli	0.000045	1.00	1.00
169	13006AA	5A	Brussels sprouts	0.000045	1.00	1.00
170	13007AA	5A	Cabbage-green and red	0.000052	1.00	0.02
171	13008AA	5A	Cauliflower	0.000045	1.00	1.00
174	13011AA	5B	Kale	0.002912	1.00	1.00
176	13013AA	4A	Lettuce-leafy varieties	0.000026	1.00	1.00
181	13018AA	O	Artichokes-globe	1.160000	1.00	0.04
182	13020AA	4A	Lettuce-unspecified	0.000026	1.00	1.00
183	13021AA	5B	Mustard greens	0.000045	1.00	1.00

Table 11. Inputs Used By Cheminova For Its Chronic Dietary Risk Assessment (continued)

Food Code	EPA Code	Crop Group	Food Name	Residue (ppm)	Adj. Fctrs #1	Adj. Fctrs #2
186	13024AA	4A	Spinach	0.000043	1.00	1.00
188	13026AA	2	Turnips-tops	0.374000	1.00	0.06
192	13045AA	4A	Lettuce-head varieties	0.000026	1.00	1.00
198	14003AA	1AB	Carrots	0.000193	1.00	1.00
205	14011AA	3	Onions-dry-bulb (cipollini)	0.000189	1.00	1.00
206	14011DA	3	Onions-dehydrated or dried	0.000189	9.00	1.00
207	14013AA	1C	Potatoes/white-whole	0.000022	1.00	1.00
208	14013AB	1C	Potatoes/white-unspecified	0.000022	1.00	1.00
209	14013AC	1C	Potatoes/white-peeled	0.000022	1.00	1.00
210	14013DA	1C	Potatoes/white-dry	0.000022	1.00	1.00
211	14013HA	1C	Potatoes/white-peel only	0.000022	1.00	1.00
219	14019AA	1AB	Turnips-roots	0.000125	1.00	1.00
227	15001AA	6C	Beans-dry-great northern	0.050000	1.00	0.02
228	15001AB	6C	Beans-dry-kidney	0.050000	1.00	0.02
229	15001AC	6C	Beans-dry-lima	0.050000	1.00	0.02
230	15001AD	6C	Beans-dry-navy (pea)	0.050000	1.00	0.02
231	15001AE	6C	Beans-dry-other	0.050000	1.00	0.02
232	15001AF	6C	Beans-dry-pinto	0.050000	1.00	0.02
233	15002AA	6B	Beans-succulent-lima	0.000093	1.00	1.00
234	15003AA	6A	Beans-succulent-green	0.000093	1.00	1.00
235	15003AB	6A	Beans-succulent-other	0.000093	1.00	1.00
236	15003AC	6A	Beans-succulent-yellow/wax	0.000093	1.00	1.00
237	15004AA	15	Corn/pop	0.057000	1.00	0.01
240	15007AA	6C	Peas (garden)-dry	0.050000	1.00	0.02
241	15009AA	6AB	Peas (garden)-green	0.000093	1.00	1.00
243	15011AB	6C	Lentils	0.050000	1.00	0.02
244	15013AA	6C	Mung beans (sprouts)	0.050000	1.00	0.02
249	15022AA	6C	Beans-dry-broadbeans	0.050000	1.00	0.02
250	15022AB	6B	Beans-succulent-broadbeans	0.000093	1.00	1.00
251	15023AA	6C	Beans-dry-pigeon beans	0.050000	1.00	0.02
253	15027AA	6	Beans-unspecified	0.000093	1.00	1.00
255	15029AA	6A	Soybeans-sprouted seeds	0.000173	0.33	1.00
256	15030AA	___	Beans-dry-hyacinth	0.050000	1.00	0.02
257	15030AB	___	Beans-succulent-hyacinth	0.000093	1.00	1.00
258	15031AA	6C	Beans-dry-blackeye peas/cowpea	0.050000	1.00	0.02
259	15032AA	6C	Beans-dry-garbanzo/chick pea	0.050000	1.00	0.02
262	16004AA	3	Onions-green	0.000189	1.00	1.00
265	24001AA	15	Barley	0.000039	1.00	1.00
266	24002EA	15	Corn grain-endosperm	0.057000	1.00	0.01
267	24002HA	15	Corn grain-bran	0.057000	1.00	0.01
268	24002SA	15	Corn grain/sugar/hfcs	0.057000	1.00	0.01
269	24003AA	15	Oats	0.000039	1.00	1.00
270	24004AA	15	Rice-rough (brown)	1.196000	0.18	0.08
271	24004AB	15	Rice-milled (white)	1.196000	0.04	0.08
272	24005AA	15	Rye-rough	0.000039	1.00	1.00
273	24005GA	15	Rye-germ	0.000039	1.00	1.00
274	24005WA	15	Rye-flour	0.000039	1.00	1.00
276	24007AA	15	Wheat-rough	0.000039	1.00	1.00
277	24007GA	15	Wheat-germ	0.000039	1.00	1.00

Table 11. Inputs Used By Cheminova For Its Chronic Dietary Risk Assessment (continued)

Food Code	EPA Code	Crop Group	Food Name	Residue (ppm)	Adj. Fctrs #1	Adj. Fctrs #2
278	24007HA	15	Wheat-bran	0.000039	1.00	1.00
279	24007WA	15	Wheat-flour	0.000039	1.00	1.00
282	25002SA	1A	Sugar-beet	0.000022	1.00	0.01
286	26001AA	15	Buckwheat	0.000039	1.00	1.00
289	27002OA	15	Corn grain-oil	0.057000	1.00	0.01
290	27003OA	O	Cottonseed-oil	1.410000	0.59	0.12
291	27003WA	O	Cottonseed-meal	1.410000	0.13	0.12
293	27007OA	O	Peanuts-oil	0.050000	1.00	0.01
297	27010OA	6A	Soybeans-oil	0.000173	2.70	1.00
298	27011OA	O	Sunflower-oil	0.200000	1.00	0.01
303	15023AA	6A	Soybean-other	0.000173	1.00	1.00
304	28023AB	6A	Soybeans-mature seeds dry	0.000173	1.00	1.00
305	28023WA	6A	Soybeans-flour (full fat)	0.000173	1.00	1.00
306	28023WB	6A	Soybeans-flour (low fat)	0.000173	1.00	1.00
307	28023WC	6A	Soybeans-flour (defatted)	0.000173	1.00	1.00
315	43058AA	O	Grapes-wine and sherry	0.001637	0.03	1.00
377	04001JC	11	Apples-juice-concentrate	0.000473	3.00	1.00
379	25002MO	1A	Sugar-beet-molasses	0.000022	1.00	0.01
383	13007SA	5B	Cabbage-savoy	0.000052	1.00	0.02
384	13002JA	4B	Celery juice	0.000220	1.00	1.00
388	24002MO	15	Corn grain/sugar-molasses	0.057000	1.00	0.01
392	01014JC	O	Grapes-juice-concentrate	0.001637	0.09	1.00
399	24003BR	15	Oats-bran	0.000039	1.00	1.00
402	05004JA	12	Peaches-juice	0.015881	1.00	1.00
403	15006BT	O	Peanuts-butter	0.050000	1.00	0.01
404	04003NA	11	Pears-juice	0.001086	0.14	1.00
405	15008AA	6B	Peas-succulent/blackeye/cowpea	0.000093	1.00	1.00
408	24004BR	15	Rice-bran	1.196000	0.70	0.08
409	24013AA	15	Rice-wild	1.196000	1.00	0.08
417	15018HA	O	Sunflower-seeds	0.200000	1.00	0.01
423	11005DA	8	Tomatoes-dried	0.000042	29.00	1.00
431	030090L	14	Walnut oil	0.050000	1.00	0.01
437	24007OL	15	Wheat-germ oil	0.000039	1.00	1.00
452	No Code	5B	Bok choy	0.000052	1.00	0.02
482	No Code	O	Soybeans-protein isolate	0.000173	1.00	1.00
940	No Code	O	Peanuts-hulled	0.050000	1.00	0.01

Acute dietary risk

EPA conducted a Tier I acute dietary risk assessment which indicated that the risk was >10,000% of the acute RfD. EPA states in the executive summary that the preliminary Tier I acute dietary risk assessment indicates unacceptable risk estimates for all population subgroups. However, EPA's policy (Acute Dietary Exposure Assessment Office Policy, dated June 1996) provides that acute exposure assessments should be conducted using a tiered approach. Under this policy, the Tier I assessment results only mean that a more realistic estimation of the risk should be conducted using higher-tier assessment procedures. Cheminova is conducting a Tier III Monte Carlo dietary assessment and will submit the results of this assessment when completed.

It is not clear why the results of EPA's acute dietary assessment are presented as percentages of the acute RfD. EPA Guidance states that acute results are to be presented as Margins of Exposure (MOEs), based on the NOEL, not the RfD. Expression of the risk as a percentage of the RfD could lead to confusion because the safety factors are included in the RfD. Therefore, Cheminova believes that EPA should follow its own guidance, under which the acute risk is presented as MOEs and not as a percentage of the RfD.

2. Drinking Water Exposure

EPA assessed potential exposure and risk from methyl parathion in drinking water from models and from limited monitoring data. For ground water, EPA used the SCI-GROW screening model and states that without groundwater monitoring data no refinement of this assessment can be made. Accordingly, EPA proposes to require a ground water monitoring study. Based on the results of the Agency's Tier II surface water assessment using the PRZM3 and EXAMS models, and a review of USGS surface water monitoring studies in California and Mississippi that measured or modeled drinking water exposures, EPA concluded that drinking water is expected to contribute very little to overall dietary exposure.

The Agency's groundwater assessment ignores both USGS ground water monitoring data and the available data from EPA's own Pesticides in Ground Water Database (PGWD, September 1992). The USGS NAWQA Program monitors pesticides in groundwater. During the period of 1992 to 1995, USGS NAWQA reported no detections of methyl parathion in groundwater, though several thousand samples were analyzed for methyl parathion at a method limit of detection of 0.006 ppb. The PGWD summarizes monitoring data from 1971

to 1991; this report summarizes data for both methyl parathion and methyl paraoxon. Methyl paraoxon was analyzed for in only 125 samples from Mississippi and California (two important states from a usage standpoint) and was never detected. Methyl parathion was detected only in 20 samples from 3,357 discrete wells sampled for methyl parathion from 1982 to 1991. Concentrations ranged from 0.01 ppb to 0.256 ppb.

The extensive monitoring for methyl parathion in groundwater from USGS NAWQA study sites across the U.S. for four years and the large body of historical monitoring data in the PGWD indicate that any potential exposure to methyl parathion in drinking water derived from ground water is extremely small. The known rapid dissipation of methyl parathion after application to terrestrial or aquatic crops precludes its survival for periods of time sufficient to allow subsurface transport to aquifers used as sources of drinking water. These data demonstrate conclusively that a ground water monitoring study of methyl parathion is not needed.

Methyl parathion in surface waters has also been extensively monitored in the USGS NAWQA Program. This program analyzed 5,218 surface water samples during the period from January 16, 1992, to December 16, 1996; methyl parathion was rarely detected. The USGS methods for methyl parathion have a method detection limit of 0.006 ppb. Only 36 detections of methyl parathion, in the range of 0.3 to 0.006 ppb, were found in the 5,218 samples (0.69%). Several of the NAWQA study units include areas where methyl parathion use is substantial, particularly the Mississippi Embayment and the San Joaquin-Tulare Basins. These USGS NAWQA data represent a much larger database than the Agency reviewed in the draft RED. Cheminova agrees with EPA that the monitoring data are reliable. However, Cheminova also notes that the rare, low-level detections in these studies are **not** in drinking water, but are from rivers, lakes, and even small streams in agricultural areas. These sources may be too small to serve as sources of drinking water; in addition, water samples from these sources have not been processed through community water system treatment plants.

The extensive monitoring for methyl parathion in surface waters from NAWQA study sites across the U.S. for five years indicates any potential exposure to methyl parathion in drinking water derived from surface water is extremely small.

Cheminova agrees with EPA's conclusion that measured or modeled drinking water exposures are expected to contribute very little to overall dietary exposure.

3. Occupational Risk

a. Application Situations of Concern to EPA

EPA contends that certain methods of application pose a potential for worker exposure to methyl parathion. EPA specifically mentions that it has concerns related to the application scenarios discussed below; Cheminova's responses are as follows:

Mixing/Loading: Cheminova believes that the combination of engineering controls and personal protective equipment required by its label significantly reduce any potential for mixer and/or loader exposure to the EC formulations of methyl parathion. Although the Mcap formulations are not required to comply with the engineering controls required for the EC formulations, the Mcap formulations are engineered to have lower rate of dermal absorption; thereby, reducing the potential of exposure to workers during mixing/loading.

Aerial applications made using less than two gallons of finished spray per acre: With the exception of cotton and grass, Cheminova is not supporting any aerial application of methyl parathion made in solutions of less than two gallons of finished spray per acre. Cheminova will amend its end-use labels to specify that aerial applications are to be made in at least two gallons of finished spray solution per acre.

Chemigation: Cheminova is not supporting the application of the EC formulation of methyl parathion through any type of irrigation system. Cheminova's end-use labels already prohibit application of the EC formulation in this manner. This application technique only permitted by Elf Atochem for it's Mcap formulation.

Use of human flaggers: Cheminova agrees that the use of human flaggers during application of methyl parathion should be prohibited. Cheminova's end-use label already includes language to prohibit the use of human flaggers during aerial application. Only Elf Atochem's end-use labels allow the use of human flaggers.

D. DATA NEEDS

1. EPA states that a developmental neurotoxicity study in rats is required. As discussed in Section A.3 above and elsewhere in these comments, Cheminova does not believe such a study for methyl parathion is warranted, based on the existing data.

2. In the EPA HIARC and Safety Factor reports (but not in the Toxicology Chapter), methyl parathion is included with a group of OPs that "require Assessment of NTE." Cheminova does not believe either that such a requirement is necessary, or that an evaluation of NTE in the absence of evaluation of other indications of potential delayed neuropathy would be scientifically sound. The bases for Cheminova's conclusions are outlined in Attachment C.

3. EPA states that a new lettuce metabolism study is required. Cheminova notes that this study was submitted on October 9, 1998 (MRID 44669501). Cheminova requests that EPA recognize the submission of this report.

4. EPA states that additional data are required to validate the experimental methods for the poultry and ruminant metabolism studies. Cheminova notes that these data were submitted on February 2, 1998 (no MRID number assigned). Cheminova requests that EPA note that these data and information were submitted and are in review.

5. EPA indicates that an independent laboratory validation of the proposed enforcement method is required. Cheminova proposes to use the FDA multiresidue testing protocol(s) as the methyl parathion enforcement method. Therefore, Cheminova believes that independent laboratory validation is not needed.

6. EPA states that data depicting the storage stability of methyl parathion residues of concern in/on a representative fruit are required. Cheminova notes that data depicting storage stability of methyl parathion residues in fruit are relevant to the Mcap formulation only. Cheminova is not supporting uses of the EC formulation of methyl parathion on fruits. In response to the April 10, 1997, DCI, Elf Atochem committed to submit the required storage stability data for representative fruit.

7. EPA states that magnitude of the residue (MOR) data are required on the following crop/commodities: aspirated grain fractions, alfalfa, almonds, apples, beans (succulent and dried), cherries, cottonseed, cotton gin byproducts, grass, hops, onions, peanuts, pears, pecans, plums, potatoes, rice straw, rape forage, sorghum, soybeans, sweet potatoes, sugar beet tops, turnip tops, and wheat. Cheminova notes that it is conducting residue studies on cotton, alfalfa, grass, and wheat AGF. These studies were requested in the April 10, 1997 DCI. Cheminova is not conducting studies on almonds, apples, cherries, hops, peanuts, pears, pecans, plums, sorghum, sweet potatoes, and rape forage because it is not supporting uses on these crops. Cheminova is not aware of any data gaps for the EC formulation on any of the Cheminova-supported crops except as noted above for the in-progress studies on cotton, alfalfa, grass, and wheat aspirated grain fractions. Cheminova believes that sufficient data are available for representative cereal grains to support a cereal grain crop group tolerance; therefore, Cheminova does not agree that residue data are required for rice straw. Elf Atochem is currently conducting and will submit residue data to support the use of the Mcap formulation on aspirated grain fractions, cotton gin byproducts, onions, pears, plums, potatoes, soybeans, and wheat. Elf Atochem proposes to conduct a residue study to support the use on sweet potato. Labels will be amended in response to a generic label data call-in issued with the RED to resolve any outstanding issues for all Cheminova- and Elf Atochem-supported crops.

8. EPA states that processing studies on peanuts, plums/prunes, and sunflower seed are required. Cheminova is conducting a sunflower processing study. Cheminova is not conducting processing studies for peanuts and plums/prunes because it is not supporting the use of the EC formulation on these crops. Elf Atochem has submitted a peanut processing study (MRID 44020303) and is currently conducting a study in processed plums/prunes.

9. Cheminova intends to conduct the required ruminant and poultry feeding studies. In response to the 1997 DCI, Cheminova submitted a protocol for these studies to EPA on October 27, 1997; however, changes to the study designs proposed in the draft HED Chapter require revisions to the protocol before the studies can be conducted. Because of these important design issues, which are discussed in detail in Attachments D and E, these studies will be conducted in 1999.

IX. CHEMINOVA'S COMMENTS ON EPA'S ATTACHMENTS

Cheminova's comments on each of EPA's attachments are provided as attachments to this document as follows:

- **Attachment A** – Cheminova's comments on EPA's *Toxicology Chapter* (Kathleen Raffaele, March 10, 1998) (EPA Attachment 2);

- **Attachment B** – Cheminova's comments on the Agency document titled *Methyl Parathion (O,O-dimethyl O-p-nitrophenyl phosphorothioate): Hazard Identification Committee Report* (George Ghali, December 1, 1997) (EPA Attachment 1);

- **Attachment C** – Cheminova's comments with respect to methyl parathion on a draft report from EPA's Hazard Identification Assessment Review Committee (HIARC) titled *Hazard Assessment of the Organophosphates* (dated July 7, 1998) and a combined report from the Food Quality Protection act (FQPA) Safety Factor Committee and the HIARC, titled *FQPA Safety Factor Recommendations for the Organophosphates* (dated August 6, 1998);

- **Attachment D** – Cheminova's comments on EPA's *Residue Chemistry Chapter for the Methyl Parathion Reregistration Eligibility Decision (RED) Document* (Bonnie Cropp-Kohlligian, June 11, 1998);

- **Attachment E –** Cheminova's comments on EPA's document titled *Methyl Parathion. The Outcome of the HED Metabolism Assessment Review Committee Meeting Held on March 11, 1998* (Bonnie Cropp-Kohlligian, May 21, 1998) (EPA Attachments 3 and 4);

- **Attachment F** – Cheminova's comments on EPA's *Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Methyl Parathion* (Jonathan Becker, March 2, 1998); and

- **Attachment G –** This attachment includes a list of the references used by Cheminova in compiling these comments, including public literature, EPA memoranda, and EPA Data Evaluation Records (DERs).

- Attachment H – **CONFIDENTIAL ATTACHMENT** – This attachment has sales information on methyl parathion and has been removed from the releasable part of this document.

X. CONCLUSIONS

Cheminova appreciates the opportunity to offer these comments and looks forward to working with EPA to resolve the many issues it has raised. Cheminova believes that consideration of its comments will reduce the Agency's concerns with regard to this compound and will lead to the conclusion that the draft HED chapter overestimates the potential risks associated with the use of methyl parathion.

<u>Attachment A</u>
Toxicology

Comments on the Toxicology Chapter for the Methyl Parathion Reregistration Eligibility Document, Dated March 10, 1998

Cheminova Agro A/S
P.O. Box 9
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40 pages

TABLE OF CONTENTS

I. INTRODUCTION

Cheminova Agro A/S (Cheminova) is commenting on the Toxicology Chapter for the Methyl Parathion Reregistration Eligibility Document (RED) (dated March 10, 1998). Cheminova will comment first on the "Uncertainty Factors/FQPA Considerations" section, including developmental and reproductive toxicity considerations, EPA's recommendation that a developmental neurotoxicity study be required for methyl parathion, and the retention of the additional 10X safety factor for methyl parathion under the Food Quality Protection Act (FQPA). Following this, Cheminova comments on EPA's review of the toxicology database for methyl parathion and discusses the derivation of endpoints for risk assessment.

II. UNCERTAINTY FACTOR/FQPA CONSIDERATION

In the section titled "Uncertainty factor/FQPA consideration" (pages 14-19 of the Toxicology Chapter), EPA is relying on various reproductive and developmental toxicity data to support retention of the additional 10X safety factor. Cheminova addresses these key data below.

EPA GUIDELINE STUDIES

Daly and Hogan, 1982 (MRID 00119087): This study showed no evidence of unique susceptibility to pups from exposure to methyl parathion. Cheminova concurs with the no-observed effect levels (NOELs) that EPA established in the study for parental and pup toxicity (approximately 0.4 mg/kg bw/day based on adult compound consumption data), based on decreased body weight gain in both adults and pups. The exposure to the pups during late lactation and early postweaning would predictably be higher on a mg/kg bw/day basis than that of the adult rats, although the data provided in the report do not allow quantification of the difference. EPA also concluded that adverse effects on pup survival occurred at the high dose level (approximately 2 mg/kg bw/day based on adult compound consumption data). Cheminova comments, however, that when pup survival is analyzed on a per litter basis, which is the scientifically accepted procedure, no clear treatment-related effect on survival is evident. The NOEL for this finding is ó 2 mg/kg bw/day.

Loser and Eiben, 1982: This study (included with this submission) has certain deficiencies, e.g., lack of adequate characterization of toxicity to adults, which would likely result in a supplementary classification and preclude an assessment of relative sensitivity of adults and pups. Decreased pup survival was seen at

50 ppm in this study (adult dose of approximately 2 to 3 mg/kg bw/day based on other dietary study data); reanalyses of pup survival data on a per litter basis shows no effect on pup survival at 10 ppm (approximately 0.6 mg/kg bw/day). Based on other subchronic and chronic toxicity data for methyl parathion, 50 ppm is a severely toxic dose to adult rats. No data were available to indicate if the decrease in pup survival was due to direct toxicity to the pups or to a failure to nurture. (See Attachment B, Cheminova's Comments on EPA's HID Document, for a more complete discussion of both reproductive toxicity studies and the results of the statistical reanalyses of pup survival.)

The overall NOEL from both reproductive toxicity studies is 5 ppm (approximately 0.4 mg/kg bw/day) for both pups and adults. These studies show no evidence of increased susceptibility of pups compared with adult animals.

Becker and Luetkemeier, 1987 (MRID 41136101): Cheminova concurs with EPA's conclusions regarding this study. Embryotoxicity (characteristic of developmental delay) was seen only at the lethal maternal dose of 3.0 mg/kg bw/day. The NOEL for both maternal and developmental toxicity was 1.0 mg/kg bw/day. There was no evidence of unique susceptibility of the fetus in this study.

Renhof, 1984 (MRID 000259403, 000259404, 000259405): Cheminova concurs with EPA that no maternal or fetal toxicity was evident in this study at a dose of 3.0 mg/kg bw/day (highest dose tested (HDT).

Hoberman, 1991: This study (included with this submission) is a guideline developmental toxicity study in rabbits that was conducted to satisfy California Department of Pesticide Registration data requirements. The study design and results are discussed in detail in the comments on the HID document. In brief, methyl parathion was administered by gavage on gestation day (GD) 6 through 18 to New Zealand White rabbits at doses of 0, 0.3, 3.0, and 9.0 mg/kg bw/day. In dams, there were no treatment-related clinical signs of toxicity or findings at gross necropsy at doses up to 9.0 mg/kg bw/day (HDT). (In contrast, in a range-finding study in pregnant rabbits, a 9.0 mg/kg bw/day dose caused extensive clinical signs.) Red blood cell (RBC) cholinesterase (ChE), assessed in dams after dosing on GD 18, was statistically significantly inhibited compared with control in all dose groups. RBC ChE inhibition in the 0.3 mg/kg bw/day dose group, however, while statistically decreased compared with control, was less than 20% decreased, and no clinical signs of toxicity were observed; thus, this dose level is considered a maternal NOEL. The NOEL for developmental toxicity in this study was 9.0 mg/kg bw/day (HDT).

In summary, guideline reproductive and developmental toxicity studies of methyl parathion show no evidence of increased susceptibility of fetuses or pups to the toxic effects of methyl parathion. Further, as acknowledged by EPA (page 18 of

Toxicology Chapter), "no evidence of abnormalities in the development of the fetal nervous system was observed in the prenatal developmental toxicity studies, at maternal doses up to 3.0 mg/kg bw/day." In the two-generation study in rats, no clinical evidence suggestive of neurotoxicity was observed grossly in pups, which had been administered methyl parathion *in utero* and during early and late post-natal development, generally mediated by maternal dietary exposure, but also available in the diet to late lactation pups.

ADDITIONAL INFORMATION FROM THE LITERATURE

EPA provides brief, uncritical reviews of several studies from the open literature. EPA does not discuss the general weaknesses of the published studies, including lack of Good Laboratory Practices (GLP) compliance, lack of dose concentration or homogeneity analyses, lack of characterization of the test substance purity, absence of individual animal data, and insufficient reporting of methodology and results. These deficiencies are critical to consider when determining how much weight should be given to the study results.

All of these studies are discussed in detail in the comments on the HID document (Attachment B). A critical review of the data on effects on gestation and morphological development following *in utero* exposure or assessment of biochemical and behavioral parameters following prenatal exposure to pups fails to demonstrate any unique fetal susceptibility to methyl parathion. There are some persistent errors in EPA's reporting of these study results, which are summarized below. Additionally, Cheminova disagrees with EPA's conclusions regarding the results of the Gupta et al.,1984, evaluation.

Fuchs et al., 1976[1]: EPA states that this study showed that methyl parathion administered to pregnant rats in the diet at 3 ppm [sic] resulted in growth retardation and increased incidence of resorptions in the treated group. The EPA summary appears to be based on the translated abstract of this German study. There are several inaccuracies in the abstract itself or in the translation of the abstract relied on by EPA. Significantly, methyl parathion was administered orally in this study as a suspension in olive oil at doses up to 3 **mg/kg bw/day** (presumably by gavage) rather than administered, as stated by EPA, in the diet at a 3 **ppm** dose level. Methyl parathion was thus administered at a 20-fold higher dose than that reported by EPA. The intervals of dosing reported in the Toxicology Chapter review and in the study abstract are also incorrect. Methyl parathion was reported in the abstract (including the original German abstract) to have been administered from days 5 to 9 and days 11 to 15 or 11 to 19. The published study report, however, states administration was done every 2 days from either days 5 to

[1] EPA incorrectly cites the year of this study. This study was published in 1976.

15 (dose levels of 0, 0.1, 1 or 3 mg/kg bw/day) or days 5 to 19 (3 mg/kg bw/day only). These intervals correspond to the tabulated data presented in the report and are most likely to be correct. Review of the actual study report shows that embryotoxicity, which included increased fetal resorptions, decreased fetal weight, and delayed ossification, was evident in this study only at 3 mg/kg bw/day. EPA did not characterize maternal toxicity in the summary of this study included in the toxicology chapter. As would be expected, the 3 mg/kg bw/day dose level was maternally toxic, as demonstrated by maternal weight loss during the gestation period and clinical signs of toxicity. This study provides corroborating evidence to the Guideline rat developmental toxicity study of methyl parathion that showed no unique susceptibility to the developing fetus from maternal exposure to methyl parathion (Becker, 1987).

Kumar and Devi, 1996[2]: The results of the study confirm the presence of fetotoxicity only at the 1.5 mg/kg bw/day dose level that caused marked maternal toxicity. The EPA Toxicology Chapter discussion of maternal toxicity for this study includes only decreased weight gain (which is also the only maternal effect described in the abstract to this paper); however, review of the complete published report shows muscle fasciculation, tremors, lethargy, and convulsions also occurred in the dams at the 1.5 mg/kg bw/day dose level.

Gupta et al., 1985[3]: This study evaluated a number of biochemical and behavioral parameters in the offspring of dams dosed with methyl parathion from day 6 to 20 of gestation at 1.0 mg/kg bw/day ingested in a peanut butter vehicle or 1.5 mg/kg bw/day by gavage in peanut oil. The design, results and interpretation of this study are discussed in detail in Cheminova's Comments on the HID document (Attachment B).

The study authors' apparent objective was to investigate physical changes in the brain tissue of pups (decreased number of receptors or morphological changes) and confirmatory neurochemical and behavioral effects. Instead, the study findings, in summary, were the following:

1. It affected acetyl cholinesterase (AChE) and choline acetyltransferase (CAT) activity (to a lesser extent in pups than in dams);

2. It caused changes in binding to cortical muscarinic receptors in dams but not in pups;

3. It caused no morphological effects in pup brains;

[2] EPA incorrectly cites the year of this study. This study was published in 1996.
[3] The study that the EPA HID document refers to here was published in 1985, not 1984. An earlier study by Gupta et al. published in 1984 is cited in the 1985 article.

4. It caused no effects in pups from either dose group in the majority of the behavioral tests; and

5. It caused changes compared with control in three behavioral tests at the low dose level, but not at the high dose level. It also caused changes in one other behavioral test at the low dose level; high dose results were not reported.

The authors admitted in the text of the article that the "lack of a clear [sic] dose response in the several behaviors affected by MPTH is disconcerting." They also noted that "although acetylcholine has a functional role in a number of behaviors, there is no obvious relationship between the observed neurochemical and behavioral alterations in the study." These factors support a conclusion that the study was negative for developmental neurotoxicity and that there were no effects on pup neurons and no treatment-related behavioral effects. However, the authors chose instead to conclude the article by asserting that prenatal exposure to methyl parathion "resulted in altered postnatal development of brain AChE and CAT activities and selected subtle alterations in behavior." In the study abstract (although not in the study text), the significance of the study results was further inflated by the claim that methyl parathion "altered postnatal development of cholinergic neurons." This conclusion, however, is not supported by the study findings.

EPA relied directly on the conclusion of the study authors and made no apparent effort to critically evaluate the study's weaknesses (which are detailed in Attachment B), nor to assess the validity of the conclusions. The Toxicology Chapter of the RED uses the Gupta et al.,1985, study as one of the primary bases for requiring that an FQPA safety factor be retained, and for requiring a developmental neurotoxicity study for methyl parathion. The inflated conclusion that methyl parathion "altered postnatal development of cholinergic neurons" is reiterated under Susceptibility Issues and Uncertainty Factor headings in the Toxicology Chapter text, despite the failure of the study results to support this conclusion. Findings in the behavioral assays do not show treatment-related adverse effects, based on both the absence of dose response and the absence of correlation to biochemical effects. Further, there is no evidence of any morphological or microscopic neural developmental abnormality in pups of dams exposed to overtly toxic doses of methyl parathion. In summary, the study results do not show evidence of developmental neurotoxicity, and they do not support the conclusion (cited repeatedly by EPA) that altered postnatal development of cholinergic neurons resulted from the prenatal exposures to methyl parathion.

On page 19 of the Toxicology Chapter, EPA states regarding the Gupta et al., 1985, study that "no indication of additional sensitivity of the offspring was suggested by the data, since offspring effects were noted concurrently with

maternal effects." Cheminova agrees with this conclusion regarding the absence of unique or additional susceptibility of the offspring in this study. However, on the same page (point number two of the Uncertainty Factor section) the Gupta et al., 1985, study is cited as providing "qualitative evidence" of "increased sensitivity to the offspring." These two statements are in direct conflict.

DIRECT ADMINISTRATION TO PUPS

The HID document includes summaries of the published studies (Benke et al., 1975[4], Pope et al., 1991, and Pope et al., 1992) in which methyl parathion is administered directly to pups at high dose levels. In general, Cheminova concurs with EPA's summaries of the tests and results. However, we do not consider that these studies provide a substantive basis for any additional safety factor based on pup susceptibility, because of the inappropriate routes of administration (intraperitoneal or subcutaneous) and high dose levels used in these studies. Comments on these postnatal studies are included in Comments on the HID report (Attachment B).

As discussed in Cheminova's Comments on the HID document (Attachment B), the primary influence on the differential susceptibility of pups and adults to methyl parathion appears to be the level or activity of detoxifying enzymes. It is not scientifically sound to use effects from high dose exposures, at which the available detoxifying enzymes are saturated, to predict effects at low levels more representative of human exposure. In the report of the March 24-25, 1998, Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Committee, the Panel suggested that:

> the magnitude and difference of the sensitivity between adults and juveniles should be determined more thoroughly . . . much of this information was generated in acute treatment experiments, frequently at very high exposure levels. Such data may not be appropriate to extrapolate to low-dose situations, e.g., organophosphates, where much, if not all, of the age-related differences may be attributable to differences in the magnitude and activity of detoxification enzymes. *In such cases, differences in toxicity between adults and juveniles would be substantially greater at high doses where detoxification mechanisms are saturated than at low dose levels where they are not* (emphasis added).

RECOMMENDATION FOR A DEVELOPMENTAL NEURO- TOXICITY STUDY

[4] EPA incorrectly cites the year of this study. This study was published in 1975.

EPA sets forth (at pages 17-18) a number of factors that it considered in "a weight-of-the-evidence" conclusion that a developmental neurotoxicity study is required. Each of these factors is addressed below.

1. EPA: Methyl parathion is a neurotoxic chemical.

Cheminova comment: At some dose level, this is true for almost all insecticides and many other chemicals.

EPA: SAR: Methyl parathion is an organophosphate chemical.

Cheminova comment: At this time EPA is not requiring developmental neurotoxicity testing for all or even most organophosphate pesticides.

EPA: Administration to various species results in ChE inhibition in the plasma, RBC, and brain.

Cheminova comment: At some dose level this is true for all organophosphates (OPs) and carbamates, some medications, and some naturally occurring compounds, e.g., solanine.

EPA: Neurobehavioral effects . . . were observed in rats in an acute neurotoxicity study at a gavage dose of 7.5 mg/kg . In the subchronic neurotoxicity study, . . . was observed at 50 ppm (3.02/3.96 mg/kg bw/day).

Cheminova comment: True. However, the acute 7.5 mg/kg dose exceeds the dose cited by EPA as the lethal dose 50% (LD_{50}), and behavioral effects were seen only at the time of peak effect on the day of dosing. Additionally, the 50 ppm dose tested in the subchronic neurotoxicity study showed evidence of systemic toxicity at the same dose, i.e., the behavioral effects were not the most sensitive measure of toxicity. (Note: Cheminova calculated the mean compound intake in the subchronic neurotoxicity study to be 3.12 or 4.05 mg/kg bw/day, for males and females, respectively.)

EPA: Neuropathological findings observed in the acute neurotoxicity study in rats (at 7.5 mg/kg) included focal demyelination of the dorsal and ventral root fibers of the cervical and lumbar spinal cord and focal demyelination of the sural and tibial nerves. In the subchronic neurotoxicity study, the incidences of degenerative lesions of peripheral nerves at 50 ppm (3.02/3.96 mg/kg bw/day in M/F) were equivocal. In the two-year chronic study in Sprague-Dawley rats,

loss of myelinated sciatic nerve fibers and retinal atrophy were observed at 50 ppm (2.5 mg/kg bw/day).

Cheminova comment: There are several misstatements and errors in this paragraph, which are addressed below.

In the acute neurotoxicity study, review of the histopathological incidence data shows a slightly increased incidence of focal demyelination at 7.5 mg/kg compared with control in male animals only, and only in the dorsal and ventral root fibers of the lumbar spinal cord (and none in the cervical spinal cord). A single incidence of focal demyelination of the tibial nerve was seen at this dose level, and no lesions of the sural nerve were evident at 7.5 mg/kg. Further, the treatment-relationship of the histopathological findings in male rats at 7.5 mg/kg is considered equivocal (see discussion in Cheminova's comments on the HID report, which is Attachment B). The effects described by EPA as occurring at the mid dose level actually were seen only at the high dose level (15 or 10 mg/kg bw/day), which was a frankly lethal dose. It should also be noted that the severe congestive response of animals to very toxic dose levels of organophosphate chemicals may result in hypoxia or ischemia, which may also result in nerve damage.

No rationale is provided for EPA's assertion that equivocal treatment-related neuropathological findings were seen at 50 ppm in the subchronic neurotoxicity study. This assertion runs counter to the opinion of the study author and pathologist, Cheminova, and EPA's data evaluation record, which clearly indicate that there are no treatment-related neuropathological effects at any dose level. In fact, the Toxicology Chapter of the RED document itself states on page 13 that "No treatment-related differences were noted in . . . or the incidences of gross and neuropathological lesions at any dose level."

In the rat two-year chronic study, treatment-related retinal atrophy was present at 50 ppm (approximately 2.5 mg/kg bw/day). No similar findings were made in a one-year study at the same dose level, which was specifically required to further elucidate this finding, suggesting that high continuous exposures of long duration are necessary to induce this finding. In the two-year study, the evaluation of the sciatic nerves was limited due to the small group sizes evaluated. The EPA summary states that loss of myelinated nerve fibers was observed at 50 ppm. EPA should indicate that this was seen in males only and should consider normal high background incidence of peripheral nerve lesions in older male rats maintained in wire mesh cages. Further, EPA fails to evaluate the treatment-relationship in light of the results from the reevaluation performed on nervous system tissues from the one-year chronic rat study. This reevaluation does not support a conclusion of treatment-related neuropathology at any dose level in the rat one-year study.

Further, Cheminova believes that findings in the chronic studies are not relevant to assessment of a developmental effect, because the time span of a chronic study far exceeds any of the developmental stages in duration.

EPA: There is evidence of the developmental neurotoxic potential of methyl parathion in the open literature.

Cheminova comments: The sole basis for this assertion is the study by Gupta et al.,1985. This study is discussed in detail above in section II.B. and in the comments to the HID document on methyl parathion (Attachment B). The Gupta et al., 1985, study suffered from numerous flaws in design and reporting. Further, the study results do not support the conclusion cited by EPA that altered postnatal development of cholinergic neurons or alterations of select behaviors of the offspring resulted from maternal exposure to methyl parathion.

EPA: Methyl parathion is extremely toxic; the oral LD_{50} in rats is approximately 4.9 mg/kg (males) and 6.3 mg/kg (females).

Cheminova comments: It is not clear why this is relevant to a need for a developmental neurotoxicity study.

EPA also summarizes the evidence that does not support requiring a developmental neurotoxicity study, including the absence of abnormalities in the developmental nervous system or clinical evidence suggestive of neurotoxicity in the guideline-quality reproductive or developmental toxicity studies. EPA does not explain why these guideline study results are not given substantially more weight than the results of the poorly designed, poorly conducted, and/or poorly reported studies in the open literature.

In summary, Cheminova believes that a weight-of-the-evidence evaluation of reliable data relevant to developmental effects or to neuropathology shows that a developmental neurotoxicity study should not be required for methyl parathion.

FQPA ASSESSMENT OF ADDITIONAL SENSITIVITY FOR INFANTS AND CHILDREN

Adequacy of data package: Cheminova concurs with EPA's statement that the Part 158 data package for methyl parathion is complete. The statement in this section that "No further testing was recommended by the Committee at this time" is at odds with the statement elsewhere that a developmental neurotoxicity study is needed.

Cheminova is currently conducting additional studies to better characterize the NOEL from acute oral (dietary) and short-term dermal exposures to methyl parathion.

Susceptibility issues: Cheminova, as stated above, concurs with EPA's conclusion that the submitted guideline-quality study data provided no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to methyl parathion.

Cheminova also concurs with EPA's statement relating to the Gupta, et al. 1985 study that: "No indication of additional sensitivity of the offspring was suggested by the data, since offspring effects were noted concurrently with maternal effects," and that "Both maternal and fetal biochemical markers are affected by treatment with 1.0 or 1.5 mg/kg bw/day from gestation days 6 through 20," although effects were less pronounced in the fetuses than in the dams. As discussed in detail above and in Attachment B, Cheminova disagrees strongly with EPA's other conclusions regarding the study findings. Cheminova believes that this study provides no evidence of either altered postnatal development of cholinergic neurons or evidence of treatment-related alteration of select behaviors of the offspring.

As discussed above, in section II.C., Cheminova does not consider that the high-dose intraperitoneal or subcutaneous studies of methyl parathion administered directly to pups provide a substantive basis for concern for the effects of methyl parathion on the young.

UNCERTAINTY FACTOR

Cheminova does not concur with EPA's conclusion that the FQPA 10-fold additional safety factor should be retained for the protection of infants and children. EPA's specific concerns, and Cheminova's responses, are summarized below:

EPA: The standard developmental and reproductive toxicity studies on methyl parathion are complete and acceptable.

Cheminova comment: We agree that the standard developmental and reproductive toxicity studies are complete and acceptable. Furthermore, these studies predict no unique susceptibility for infants and children.

EPA: Although delayed neuropathy was not observed in a study in hens, a single-dose acute neurotoxicity study in rats demonstrated neuropathology at a relatively low dose level (7.5 mg/kg).

Cheminova comment: It is not clear why the negative findings for the delayed neuropathy hen study are cited in this context. It is correct that no delayed neuropathy has been seen in animal studies with methyl parathion, including in hens. The time course, progression, and severity typical of delayed neuropathy, however, do not correlate with the neuropathological findings in the methyl parathion acute study, which showed no delayed onset and no functional motor deficits. As Cheminova comments in Attachment C, EPA appears to be blurring the distinction between delayed neuropathy and the presence of any neuropathological lesions, regardless of severity or functional correlates. Cheminova considers this lack of differentiation not grounded in sound science and likely to create confusion and unnecessary concern.

As noted elsewhere in this document, the neuropathological findings at 7.5 mg/kg in the acute neurotoxicity study were less than described by EPA, were equivocally treatment-related, and were accompanied by severe toxicity (7.5 mg/kg actually exceeds the level EPA indicates is the oral LD_{50} for methyl parathion). Thus, no concern regarding neuropathological or irreversible neurotoxicity at "low levels" is justified by the results of this study. The EPA HID document for methyl parathion incorrectly indicates that effects were seen in this study at 2.5 mg/kg (a dose not tested in the study), and goes on to state that neuropathology was observed at a relatively low dose level. Apparently, even though the actual dose tested was three-fold higher, the conclusion that this was "a relatively low dose level" persisted in other EPA documents.

EPA: There was evidence of the developmental neurotoxic potential in the open literature (Gupta et al., 1985); in this study altered postnatal development of cholinergic neurons and alteration of select behaviors of the offspring resulted following *in utero* exposure.

Cheminova comment: This study is discussed at length in Attachment B. In summary, the study presents no evidence of effects on neuronal development, cholinergic or otherwise, in the offspring, although the study abstract does contain what appears to be a purely speculative conclusion to that effect. The study shows that effects on neuronal receptors (3H-QNB binding) were seen in

the dams, but those effects were found not to occur in pups. There was no evidence of morphological effects on the nervous system in pups.

Most of the behavioral tests showed no effect at either dose level tested; in three of the tests differences from control were observed at the low dose but not at the high dose— the opposite of the pattern of effects on cholinesterase activity, maternal clinical signs, and changes in other biochemical markers. No convincing explanation for this disparity or for the lack of dose response is offered by the authors. A variety of serious weaknesses in the study design and reporting could easily account for the purported low-dose effects.

EPA: A developmental neurotoxicity study of methyl parathion is needed.

· *Cheminova comment: We disagree, for the reasons outlined in Section II. D. of this document and in Attachment B.*

EPA: In the absence of a developmental neurotoxicity study, substantial uncertainties exist about the potential effect of methyl parathion on functional development.

Cheminova comment: Once it is recognized that the Gupta et al.,1985, study provides no evidence of developmental neurotoxicity, there is no evidence warranting more concern about methyl parathion than about any other compound with regard to potential effects on development.

EPA (implicitly): It is appropriate to simultaneously declare the need for a new data requirement (e.g., the developmental neurotoxicity study) and to impose a regulatory penalty on registrants for having failed to satisfy it.

Cheminova comment: We disagree, for the reasons set forth in the June 1998 Implementation Working Group (IWG) Issue Paper on The FQPA Additional Uncertainty Factor.

EPA: There is qualitative evidence from the open literature of increased sensitivity to perinatal rats directly exposed to methyl parathion, as indicated by lethality at or near the maximum tolerated dose or cholinesterase inhibition at lower dose levels. Four published studies on methyl parathion are cited; in addition, a general argument is made on the basis of an unreferenced study on chlorpyrifos.

Cheminova comment: Differences between young and mature animals are "quantifiable," to the extent that none of these studies show that the standard 10X intraspecies factor is insufficient to protect infants or young.

Further, EPA's argument ignores the fact that although immature animals' more limited ability to metabolize some compounds may be overwhelmed by high doses of cholinesterase-inhibiting compounds, these animals are likely to have sufficient metabolic capacity to handle lower, more relevant dose levels to the same extent as adult animals.

Data from studies with subcutaneous or intraperitoneal injection as the route of administration are of no relevance to potential human exposure situations. Therefore, these data cannot be used for quantitative risk assessment and should not be used as the basis for an additional safety factor.

As to Pope et al., 1991: This test used subcutaneous injection, and found the MTD of 7-day-old rats to be 7.8 mg/kg, ~ 2x lower than adults.

As to Pope and Chakraborti, 1992: This test used subcutaneous injection, and found the ED_{50} of neonatal rats to be ~ 9x lower than adults.

As to Benke and Murphy, 1975: The study was done at LD_{50} doses. Further, this study used intraperitoneal injection administration, which in itself may be stressful or lethal to neonatal pups. No controls were tested in this study. The reported LD_{50} of one-day-old pups was approximately less than 10-fold lower than that of older animals.

As to Gupta, 1985: It is not clear why this study is cited in the context of direct exposure to prenatal rats. This study evaluated effects of prenatal exposures to dams. Further, in no case did pups show increased sensitivity to effects also measured in dams. Maternal brain cholinesterase activity was clearly affected in a dose-dependent manner at both dose levels; to the extent the measurement in pups can be compared with the dams, it does not appear the inhibition of cholinesterase activity is more significant in the pups than in the dams.

As to the reference to chlorpyrifos: The chlorpyrifos data are irrelevant to a hazard evaluation for methyl parathion. There is no scientific basis for relying on chlorpyrifos data in a methyl parathion hazard assessment, because chlorpyrifos is not structurally similar to methyl parathion and has a different pattern of toxicity.

III. TOXICOLOGY DATABASE

EPA asserts that the toxicology database for methyl parathion is complete, pending submission of a developmental neurotoxicity study. This contradicts the statement on page 18 of the Toxicology Chapter which states "the data package included an acceptable 2-generation reproduction study in rats and acceptable prenatal developmental toxicity studies in rat and rabbits, meeting the basic data requirements as defined for a food use chemical by 40 CFR Part 158. *No further testing was recommended by the committee at this time*" (emphasis added). Cheminova believes that the developmental neurotoxicity study requirement is not warranted, as discussed above. Cheminova is conducting further studies to better characterize the NOEL from acute dietary exposure and from short-term dermal exposure.

Determination of NOELs and NOAELs

Regarding determination of NOELs and NOAELs for ChE inhibition, Cheminova has evaluated the toxicity studies according to criteria recently developed by the Joint Meeting on Pesticide Residues (Joint Meeting on Pesticides/World Health Organization (JMPR/WHO), 1998). The key thinking supporting these criteria are as follows:

- It is well established that the signs and symptoms of organophosphorus (OP) toxicity result from inhibition of acetylcholinesterase (AChE) in the peripheral (somatic and autonomic) and central nervous systems. Consequently, overt clinical cholinergic signs constitute the most relevant endpoints for establishing NOAELs on which to base Reference Doses (RfDs).

- Inhibition of AChE measured in the nervous system, even in the absence of clinical signs might reasonably be treated as adverse if it is statistically significant and exceeds 20%. In the past, most nervous system AChE measurements in animals have been restricted to measurements using brain tissues. More recently, EPA has suggested that measurements in peripheral tissues (heart, diaphragm, neuromuscular junction, etc.) might also be required. The problem with using these tissues is that appropriate methodologies to measure AChE have not yet been developed or validated and little or no information is available with respect to species differences or other sources of variability. EPA has issued no guidance on what assays might be useful or acceptable to evaluate effects on peripheral nerve AChE, should such assays be required.

- In addition to inhibiting the AChEs in the nervous system, OP compounds also inhibit cholinesterases (ChE) present in the blood. One of these enzymes, pseudo-ChE or butyryl-ChE (BuChE) is present in the plasma, while the other, AChE, is associated mainly with the red blood cells (RBC).

- BuChE exhibits several properties that clearly distinguish it from the AChE in the nervous system. It is both structurally and biochemically distinct from AChE, hydrolizing butyrylcholine at a faster rate than ACh (the preferred substrate for AChE) and, furthermore, it plays no role in cholinergic transmission in the nervous system. For these reasons, the consensus of scientific opinion and the position adopted and recently confirmed by JMPR/WHO, is that inhibition of BuChE is not an "adverse" effect and NOELs based on this endpoint should never be used to establish an RfD (JMPR/WHO, 1998).

- RBC AChE is biochemically similar to, if not identical with, the AChE in the nervous system. However, it is important to emphasize that, while its true physiological function remains unknown, RBC AChE plays no role in nerve transmission and its inhibition, like that of BuChE, cannot be considered an "adverse" effect. Consequently, inhibition of RBC AChE provides a NOEL but not a NOAEL and should not be used as a basis for an RfD except in the absence of adequate data (showing clinical signs or inhibition of AChE) from the nervous system. Under these conditions, a statistically significant inhibition of RBC AChE that exceeds 20% may constitute the basis for an RfD.

However, Cheminova is unclear about the current JMPR/WHO position on whether peripheral nervous system AChE data is needed in addition to brain AChE data in order to be adequate, and on whether RBC AChE levels should be used as a surrogate if specific peripheral nervous system AChE data are not available. No peripheral nervous system AChE data are available for methyl parathion, as far as Cheminova is aware.

For these reasons, Cheminova's evaluation of NOEL and NOAEL levels for cholinesterase inhibition presented in the documents in this submission uses a conservative interim approach until this issue is better clarified. Under this interim approach, RBC AChE values are used to provide a surrogate measure that is protective for potential inhibition of peripheral nerve AChE. Thus, in cases where AChE inhibition is the driving effect, if (A) a study evaluated both brain and RBC AChE, but not peripheral nervous system AChE, and (B) animals at a certain dose level showed no clinical signs of cholinesterase inhibition and no significant inhibition of brain cholinesterase (as defined above), but the animals did show significant inhibition of RBC AChE (as defined above), then the RBC AChE endpoint would be treated as the LEL (and the next lower dose would be treated as a NOEL) for endpoint selection purposes. Cheminova wants to emphasize, however, that this is an interim position that we will reevaluate once the JMPR/WHO position becomes clearer.

Cheminova also considers it important to evaluate the consistency of findings between studies, particularly when reviewing older studies in which variations in cholinesterase methodology were probable, but not quantifiable. In some cases in which the RBC

cholinesterase inhibition slightly exceeds 20% but there is no evidence of statistically significant brain cholinesterase inhibition, or brain cholinesterase levels were not evaluated, Cheminova considers that clinical signs may provide more reliable evidence of an adverse effect.

Finally, Cheminova believes that the entire June 1998 IWG Issue Paper entitled "Choice and Use of Endpoints in Risk Assessments of Cholinesterase Inhibitors" is relevant to methyl parathion and that the principles it contains should be used by EPA in the evaluation of this compound.

A. ACUTE TOXICITY

EPA did not consider several acute toxicity studies (included in Cuthbert and Carr, 1986 (MRID 40364102)) conducted with methyl parathion 80% technical which were submitted to the Agency on October 2, 1987. The identification and results of the acute studies not considered by EPA are provided in Table A-1, below. These studies should be considered by EPA and included in the Toxicology Chapter.

Table A-1: Summary of Acute Toxicity Studies Not Considered by EPA[1]

Study	Results (95% Confidence Limits)
Acute oral toxicity in rats	Males: LD_{50}=25 mg/kg (21-30 mg/kg) Females: LD_{50}=62 mg/kg (47-82 mg/kg)
Acute dermal toxicity in rats	Males: LD_{50}=483 mg/kg (427-546 mg/kg) Females: LD_{50}=481 mg/kg (437-529 mg/kg)
Primary Dermal Irritation in Rabbits	Slight to moderate erythema at 1 and 24 hours with 1/6 animals showing very slight edema at 1 hour only
Primary Eye Irritation in Rabbits	Slight redness at 1 hour only; all eyes except 1 were normal by 24 hours
Dermal Sensitization in Guinea Pigs	Sensitizer

[1]Cuthbert and Carr, 1986 (MRID 40364102)

Further, Cheminova is submitting to EPA additional dermal acute toxicity data (see Attachment B).

In addition, references (and MRID numbers in some cases) for each of the studies listed by EPA were not included in EPA's tabulated data, making it difficult to verify the data presented. Confidence limits (which are important for evaluating the consistency of the results, and for comparing results for two different materials) for the LD_{50} values were also not included in EPA's Acute Toxicity Data table on page 2.

It is not clear why EPA included text summaries only for the two acute inhalation studies and none for the other acute toxicity studies shown in the table on Page 2 of the Toxicology Chapter.

EPA should cross-reference the acute delayed neurotoxicity study in hens in the table on page 2 to the study review discussion presented in the Neurotoxicity section on page 12.

B. SUBCHRONIC TOXICITY

1. Subchronic toxicity in mice

Daly and Rinehart, 1980a (MRID 00072513)
Test Material: 93.65% Purity
Dose Levels: 10.0, 30.0, 60.0 ppm

EPA indicated that histopathology was not conducted in this study; however, very limited histopathological evaluations were conducted.

2. Subchronic toxicity in rats

Daly and Rinehart, 1980b (MRID 00074299)
Test Material: 93.65% Purity
Dose Levels: 2.5, 25.0, 75.0 ppm

Cheminova disagrees with EPA's conclusion that the NOEL for systemic effects was 2.5 ppm (0.16 mg/kg bw/day for males and 0.12 mg/kg bw/day for females) based on stomach lesions at 25 ppm (1.24 mg/kg bw/day for males; 1.55 mg/kg bw/day for females). The conclusion by EPA that treatment-related microscopic stomach lesions (acanthosis and hyperkeratosis in the cardiac region) were noted in the mid dose (25 ppm) males and females is questionable for the following reasons: 1) similar treatment-related microscopic stomach lesions were not noted in two chronic rat studies that tested doses twice as high (50 ppm – approximately 2.5 mg/kg bw/day); 2) the degree of severity of the stomach lesions in the males and females at 25 ppm was minimal; and 3) control females had a relatively high background incidence. In addition, in EPA's data evaluation record of this study, EPA did not conclude that there were treatment-related stomach lesions at 25 ppm (mid dose).

EPA considers 25 ppm (1.24 mg/kg bw/day for males; 1.55 mg/kg bw/day for females) as a lowest observed effect level (LOEL) for hematological effects; however, Cheminova believes that the 25 ppm dose level is a no observed adverse effect level (NOAEL) for hematological findings based on the lack of

consistency in this finding at this dose level (hemoglobin marginally decreased; no effect on RBC or hematocrit).

EPA concludes that the NOEL for cholinesterase inhibition is 2.5 ppm (0.16 mg/kg bw/day for males; 0.12 mg/kg bw/day for females); Cheminova concurs with this NOEL based on statistically significantly decreased RBC and brain cholinesterase activity at 25 ppm.

3. Subchronic toxicity in dogs

Underwood and Tegeris, 1978 (MRID 00072512)
Test Material: 94.3%
Dose Levels: 0.3, 1.0, 3.0 mg/kg bw/day

Cheminova disagrees with EPA's conclusion that the NOEL for systemic effects was 1.0 mg/kg bw/day based on decreased pulse rate in females at 3.0 mg/kg bw/day. EPA did not include a discussion regarding the biological significance of this finding. The following questions need to be considered in determining whether or not decreased pulse rate is a treatment-related effect in this study: 1) what was the variability of this parameter in the groups; and 2) what were the experimental conditions in which pulse rate was measured for each group (i.e., were any precautions taken to minimize stress in the dogs and were conditions of restraint and measurements consistent).

Unless measurements were taken consistently and rigorous procedures were followed to minimize variability (which is doubtful), pulse rate changes are an unreliable finding that should not be considered in establishing a systemic NOEL in this study. For reference, a Danish Contract laboratory, Scantox[5], has measured pulse rate in 367 female control dogs at ages between 3 and 16 months. They found an average rate of 137 beats per minute (bpm) with a standard deviation of 25 and a range from 70 to 220 bpm. Based on the historical average of 137 bpm, the pulse rate of 121 bpm in the high dose females at 13 weeks is not significantly different.

There are no apparent treatment-related effects in this study other than cholinesterase inhibition. Cheminova thus believes that the systemic NOEL for endpoints other than cholinesterase inhibition is 3.0 mg/kg bw/day (HDT).

EPA concludes that the NOEL for RBC and plasma cholinesterase inhibition is 0.3 mg/kg bw/day and the NOEL for brain cholinesterase is 1.0 mg/kg bw/day; Cheminova concurs with these NOELs based on statistically significantly

[5] Scantox Laboratory. 36 A Hestehavevej, DK 4623, L1. Skensved.

decreased brain cholinesterase activity at 3.0 mg/kg bw/day and moderately decreased (~38% compared with controls) RBC cholinesterase activity at 1.0 mg/kg bw/day.

Daly, 1989 (MRID 41335401)
Test Material: 94.9% Purity
Dose Levels: 0.03, 0.3, 3.0 mg/kg bw/day

EPA concludes that the NOEL for cholinesterase inhibition is 0.3 mg/kg bw/day; Cheminova concurs with this NOEL based on statistically significantly decreased brain cholinesterase activity and marginally inhibited (18% to 23% compared with controls) RBC cholinesterase activity at 3.0 mg/kg bw/day (there was no correlation with clinical signs related to cholinesterase inhibition in animals at 3.0 mg/kg bw/day).

4. Dermal toxicity in rabbits

Goad, 1992 (MRID 42263701)
Test Material: 99.3% Purity
Dose Levels: 1.0, 5.0, 10.0, 100.0 mg/kg bw/day

EPA concludes that the NOEL for cholinesterase inhibition is 5 mg/kg bw/day; Cheminova concurs with this NOEL based on RBC cholinesterase inhibition at 10 mg/kg bw/day (30% to 38% compared with controls). Brain cholinesterase was not evaluated. No clinical signs of cholinesterase inhibition were observed.

C. CHRONIC TOXICITY AND CARCINOGENICITY

1. Chronic toxicity in dogs

Ahmed and Sagartz, 1981 (MRID 00093895)
Test Material: 93.7% Purity
Dose Levels: 0.03, 0.1, 0.3 mg/kg bw/day

Cheminova agrees with EPA's conclusion that the systemic NOEL in this study is 0.3 mg/kg bw/day (HDT).

EPA concludes that the NOEL for RBC and plasma cholinesterase inhibition is < 0.03 mg/kg bw/day and that the NOEL for brain cholinesterase is 0.3 mg/kg bw/day (HDT). Cheminova concurs that the NOEL for brain cholinesterase is 0.3 mg/kg bw/day; however, Cheminova believes the NOAEL for RBC cholinesterase inhibition is very close to 0.3 mg/kg bw/day. RBC cholinesterase inhibition at all dose levels was slightly decreased (19% to 32%

compared with controls). However, this finding was not dose-related and there was no correlation with clinical signs related to cholinesterase inhibition. A NOAEL of 0.3 mg/kg bw/day for RBC cholinesterase inhibition was confirmed in a recently completed 1-year dog study, which is summarized below.

New study not yet considered by EPA (Hatch, 1998 chronic dog toxicity study) (MRID 44674201)
Test Material: 95.8% Purity
Dose Levels: 0.3, 1.0, 3.0, 3.0, 3.5, 4.0 mg/kg bw/day

Cheminova recently submitted to EPA a one-year chronic toxicity study in dogs with methyl parathion (Hatch, 1998) that has not yet been reviewed by HED and that was not considered in the draft methyl parathion HED RED. This study was requested by the California Department of Pesticide Regulation (CDPR) to address California's concerns regarding ocular toxicity in a previous 13-week dog study (Daly, 1989). Therefore, this study was designed specifically to evaluate whether any treatment-related effects on intraocular pressure (IOP) would occur during a chronic study or after a 3-month exposure period followed by a 30-day recovery period. The study design otherwise corresponded to FIFRA Guideline No. 83-1. For the first 14 weeks of this study, methyl parathion was administered to six groups of beagle dogs (four per sex) at dietary concentrations equivalent to 0 (control), 0.3, 1.0, 3.0, 3.5, and 4.0 mg/kg bw/day. For the remainder of the study (from week 15 on), methyl parathion continued to be administered to five groups of dogs at dietary concentrations equivalent to 0, 0.3, 1.0, 3.5 (females), and 4.0 mg/kg bw/day (males) (four per sex per group except six per group at the high-dose level). (At approximately 3 months, two out of four males from the 3.5 mg/kg bw/day group were reassigned as "spares" to the 4.0 mg/kg bw/day, and two out of four females from the 4.0 mg/kg bw/day group were reassigned as spares to the 3.5 mg/kg bw/day for the remainder of the study.)

After 3 months on study, the 3.0 mg/kg bw/day group was placed on recovery (given untreated diet) for 30 days. This group was designed to mimic the study design for the prior 13-week dog study (Daly, 1989).

The animals were observed for clinical signs of toxicity, and body weight was measured weekly. Food consumption was measured every day and reported weekly throughout the study. At pretest and at 3, 6, and 12 months, intraocular pressures, electroretinograms, and ophthalmoscopic examinations were conducted on all dogs. In addition, for the recovery group and control animals, intraocular pressure was also measured at the end of the 30-day recovery period. Clinical chemistry, hematology, and urinalysis evaluations were conducted at pretest and at 3, 6, and 12 months on all dogs. Plasma and RBC ChE activity was measured in all dogs at pretest and at 1, 3, 6, and 12 months.

In addition, brain cholinesterase activity (in caudate nucleus, hippocampus, and cerebellum) was measured in all dogs at study termination. Macroscopic and microscopic evaluations of selected tissues were conducted on all dogs at termination.

There were no treatment-related effects on survival, food efficiency, hematologic and urinalysis findings, ophthalmoscopic findings, intraocular pressures, or electroretinograms in any dose group.

In the 3.0 mg/kg bw/day dogs that were treated for 3 months before a 30-day recovery period, treatment-related effects were limited to decreased RBC cholinesterase activity. In the dogs that served as range-finding dogs for 3 months prior to reassignments to other groups, one of the 3.5 mg/kg bw/day males had treatment-related increased incidence of diarrhea, thinness, and decreased body weight; RBC cholinesterase activity was also decreased. Treatment-related effects in the 4.0 mg/kg bw/day range-finding females included increased incidence of diarrhea in three dogs; decreased body weight in two of these three dogs; and thinness, tremors, salivation, and decreased activity in one of these latter two dogs. The 4.0 mg/kg bw/day females also had decreased RBC cholinesterase activity. There were no treatment-related adverse effects on hematological parameters in this study. Decreased serum concentrations of calcium, total protein, albumin, and globulin were seen at 3 months; these findings did not correlate with clinical signs of toxicity or with any pathological findings. Similar findings in the lower dose groups were not statistically significant, were of small magnitude, did not persist to the 12-month evaluation, and are considered not toxicologically or clinically relevant.

In dogs that were on study for the full 12 months, treatment-related effects noted in 4.0 mg/kg bw/day male dogs included diarrhea, decreased body weight with thinness (two dogs), decreased food consumption, decreased cholinesterase (at all intervals, including brain cholinesterase at termination), and thymic lymphoid depletion in the two dogs with weight loss. The 1.0 mg/kg bw/day males had only decreased mean RBC cholinesterase activity (39% to 50% compared with controls) at all intervals evaluated. The 0.3 mg/kg bw/day males had only slightly decreased mean RBC cholinesterase activity (21% compared with controls) only at a single interval (12 months). The NOEL for effects on brain cholinesterase levels or on clinical signs of toxicity is 1.0 mg/kg bw/day. The NOEL for RBC cholinesterase inhibition in males in this study is 0.3 mg/kg bw/day.

In the 3.5 mg/kg bw/day females treated for 12 months, treatment-related effects included decreased cholinesterase activities (at all intervals, including brain cholinesterase at termination). One high-dose female showed transient

seizure activity; the treatment relationship of this finding is uncertain. (The seizures observed were not characteristic of those associated with OP exposure, reversed on administration of phenobarbitol, and were not accompanied by any clinical signs of cholinesterase inhibition.) The 1.0 mg/kg bw/day females had decreased RBC cholinesterase activity (32% to 45% compared with controls) at 3, 6, and 12 months. The 0.3 mg/kg bw/day females showed no treatment-related decreases in cholinesterase activity. The NOEL for effects on brain cholinesterase levels or on clinical signs of toxicity is 1.0 mg/kg bw/day. The NOEL for RBC cholinesterase inhibition in females in this study is 0.3 mg/kg bw/day. (Refer to Tables A-2 and A-3 for RBC and brain cholinesterase results, respectively.)

Table A-2. Mean Red Blood Cell Cholinesterase Results (Percent Inhibition Compared With Controls)

Dose Level[a] (mg/kg bw/day)	Red Blood Cell (mM/L)				
	Pretest	1 Month	3 Months	6 Months	12 Months
MALES					
0	3.3	3.6	3.8	3.2	3.3
0.3	3.0	3.3 (8%)	3.0 (21%)	3.0 (6%)	2.6 (21%)*
1.0	2.7	2.2 (39%)*	1.9 (50%)**	2.0 (38%)**	1.7 (48%)**
3.0	3.0	1.2 (67%)**	1.1 (71%)**	NA[b]	NA
3.5	3.2	1.0 (72%)**	1.1 (71%)**	NA	NA
4.0	3.1	1.0 (72%)**	1.1 (71%)**	0.9 (72%)**	0.8 (76%)**
FEMALES					
0	2.6	2.7	2.5	2.9	2.5
0.3	2.7	2.4 (11%)	2.4 (4%)	2.3 (21%)	2.1 (16%)
1.0	2.6	2.5 (7%)	1.7 (32%)	1.6 (45%)	1.5 (40%)**
3.0	3.0	1.0 (63%)	1.0 (60%)	NA	NA
3.5	3.4	1.0 (63%)	0.9 (64%)	0.8 (72%)**	0.9 (64%)**
4.0	2.8	1.0 (63%)**	1.0 (60%)	NA	NA

[a] n=4

[B] NA=Not applicable

* statistically significant (pó0.05)

** statistically significant (pó0.01)

Table A-3. Mean Brain Cholinesterase Results (Percent Inhibition Compared With Controls)

Dose Level[a] (mg/kg bw/day)	Brain (mM/g)		
	Caudate Nucleus	Hippocampus	Cerebellum
MALES			
0	0.054	0.005	0.003
0.3	0.049 (9%)	0.005	0.002 (33%)
1.0	0.049 (9%)	0.005	0.003
3.0	NA[b]	NA	NA
3.5	NA	NA	NA
4.0	0.011 (80%)**	0.002 (60%)	0.001 (67%)
FEMALES			
0	0.055	0.005	0.004
0.3	0.071	0.005	0.004
1.0	0.050 (9%)	0.004 (20%)	0.003 (25%)
3.0	NA	NA	NA
3.5	0.005 (91%)*	0.002 (60%)	0.001 (75%)
4.0	NA	NA	NA

[a] n=4

[b] NA=Not applicable

* statistically significant (pó0.05)

** statistically significant (pó0.01)

2. Chronic toxicity/carcinogenicity in rats

Bomhard et al., 1981 (Accession Nos. 00257513, 00257514)
Test Material: 94.8% Purity
Dose Levels: 2.0, 10.0, 50.0 ppm

EPA concludes that the NOEL for cholinesterase inhibition in this study is 2 ppm (0.09 mg/kg bw/day for males; 0.14 mg/kg bw/day for females). Cheminova concurs with this NOEL based on statistically significant brain cholinesterase inhibition (22% compared with controls) in males at 10 ppm (0.46 mg/kg bw/day for males; 0.71 mg/kg bw/day for females). RBC cholinesterase inhibition at 10 ppm was only marginally decreased (18% to 25%) compared with controls. Cheminova disagrees that there were treatment-related effects on the liver at 10 ppm. There was an increased incidence of ORO-positive material in the liver cytoplasm of males at 50 ppm; however, the incidence of this finding at 10 ppm was low (5/50 compared to a control incidence of 2/50), and no treatment-related effect on liver enzymes was seen at this dose level. The systemic NOEL for effects other than ChE inhibition should be 10 ppm, based on decreased plasma protein at 50 ppm. Cheminova agrees with EPA's conclusion that this study noted no evidence of carcinogenicity.

Daly and Hogan, 1983 (Accession Nos. 00252501, 00252502, 00252503, 00253346, 00253372, 00253373, 00253374)
Test Material: 93.65% Purity
Dose Levels: 0.5, 5.0, 50.0 ppm

Cheminova concurs with the EPA conclusion that 50 ppm (2.63 mg/kg bw/day for males; 3.53 mg/kg bw/day for females) caused significant clinical signs (abnormal gait in females; increased aggressiveness in males); brain ChE inhibition; and an increased incidence of retinal degeneration (females). RBC cholinesterase was not decreased more than 20% compared to control at the high dose.

EPA states the following were seen at 5 ppm (0.26 mg/kg bw/day for males, 0.32 mg/kg bw/day for females): neuropathological effects; systemic toxicity (abnormal gait in females and effects on hematological parameters in males; and RBC cholinesterase inhibition.) Cheminova believes that these findings are unlikely to represent adverse treatment-related effects, for the following reasons:

- Abnormal gait was observed at a single incidence. A single occurrence of any finding in a group of 50 animals should not be used to establish an effect level. Additionally, as discussed in Attachment B, this female showed abnormal gait later in the study (at 78 weeks) than the high dose group females (at 48 weeks); females in both control and treated groups had an exceptionally high incidence of pituitary tumors, which may cause abnormal gait; and the observation was based on cage side evaluation only (in wire mesh caging).

- Hematological parameters: In males, hematological were within the normal range for older rats (which show a tendency toward anemia). Additionally, the high incidence of intercurrent infection in these animals may have skewed the evaluation of these parameters.

- RBC cholinesterase inhibition: RBC cholinesterase was not statistically significantly decreased compared to control (additionally, RBC cholinesterase was only 11% decreased compared to control).

- Neuropathological effects: Cheminova believes that the incidence of sciatic nerve lesions is not increased in females and that effects on high-dose males are equivocal. These issues are discussed in detail in Attachment B. In brief, females showed no lesions of the proximal sciatic nerve and no suggestion of a dose response for distal sciatic nerve lesions. Males

generally show an increase in the severity and incidence of lesions at 50 ppm. But the small numbers evaluated and the high background incidence of sciatic nerve lesions reported for male rats housed chronically in wire mesh caging makes ascription to methyl parathion exposure equivocal. Males in the mid dose group showed no clearly treatment-related increase in either distal or proximal sciatic nerve lesions. Additionally, the lack of treatment-related effects on peripheral nerves in the subchronic neurotoxicity study, as well as the neuropathological reevaluation showing no treatment-related effects in the 1-year special rat chronic study, should be considered by EPA to assist in determining the treatment relationship of the chronic study findings. Cheminova believes that the NOEL for males for equivocally treatment-related peripheral nerve lesions in this study should be at least 0.2 mg/kg bw/day, and the overall NOAEL for the study is 0.2 mg/kg bw/day.

Cheminova agrees with EPA's conclusion that this study noted no evidence of carcinogenicity. In addition, Cheminova notes that EPA does not mention that at least 50% of the animals had interstitial pneumonia in this study, which may have compromised the evaluation of the chronic toxicity of methyl parathion.

Cheminova notes there is a discrepancy in the Toxicology chapter regarding the NOEL for sciatic nerve degeneration (on page 17 versus page 7). This discrepancy probably originated with an early Data Evaluation Record (DER) for this study. As discussed below, evaluation of the treatment relationship of the neuropathological lesions for methyl parathion has gone through several steps and revisions.

3. Chronic toxicity/carcinogenicity in mice

Eiben, 1991 (MRID 42216401)
Test Material: 95.5% Purity
Dose Levels: 1.0, 7.0, 50.0 ppm

EPA concludes that the NOEL for cholinesterase inhibition is 1 ppm (0.2 mg/kg bw/day for males; 0.3 mg/kg bw/day for females). Cheminova concurs with this NOEL based on brain cholinesterase inhibition at 7 ppm. Cheminova concurs with EPA that there was no evidence of carcinogenicity in this study.

DEVELOPMENTAL TOXICITY

(See also discussion above in Section II.A. and detailed discussions of specific studies in Attachment B).

1. Developmental toxicity in rats

Becker et al., 1987 (MRID 41136101)
Test Material: 97.0% Purity
Dose Levels: 0.3, 1.0, 3.0 mg/kg bw/day; and
Becker, 1991 (MRID 42235601)
Test Material: 97.0% Purity

Cheminova concurs with the EPA evaluation of these studies, with one exception. As discussed in Attachment B, Cheminova believes that the treatment-relationship of the increased post-implantation loss at the high dose level is equivocal.

Machemer, 1977 (MRID No. 00143747)
Test Material: 94.4% Purity
Dose Levels: 0.1, 0.3, 1.0 mg/kg bw/day

In addition to the above study, Cheminova identified an earlier rat developmental study that was not reviewed in the EPA Toxicology Chapter. A summary of this study is provided in Attachment B. This study had numerous deficiencies in reporting; however, it is clear from the available data that fetal toxicity (decreased body weight) was evident only in the presence of maternal toxicity.

2. Developmental toxicity in rabbits

Renhof, 1984 (Accession Numbers 00259403, 00259404, and 00259405);
Test Material: 95.7% Purity
Dose Levels: 0.3, 1.0, 3.0 mg/kg bw/day
and Renhof 1987 a and b (MRIDs 41199001 and 41046101)

These studies appear to be the methyl parathion rabbit developmental toxicity study that is referenced by EPA only as "a developmental toxicity study in rabbits, MRID unknown." Cheminova agrees with EPA's conclusions regarding the results of this study.

Hoberman, 1991 (no MRID)
Test Material: 95.7% Purity
Dose Levels: 0.3, 3.0, 9.0 mg/kg bw/day

A second developmental study in rabbits (copy included with this submission) was conducted to meet California Department of Pesticide Registration requirements, as discussed earlier in this Attachment and in Attachment B. This study showed no developmental toxicity at 9.0 mg/kg bw/day (HDT).

E. REPRODUCTIVE TOXICITY

(See also discussion above in Section II. A. and detailed discussions of specific studies in Attachment B.)

Daly and Hogan, 1982 (MRID 00119087)
Test Material: 93.65% Purity
Dose Levels: 0.5, 5.0, 25.0 ppm

Cheminova generally concurs with EPA's conclusions regarding this study. However, as discussed previously and in Attachment B, the data do not show a clear treatment-related effect on pup survival when analyses are done on a per litter basis as recommended in EPA's reproductive toxicity risk assessment guidance; when statistical reanalyses of pup survival on a per litter basis are submitted with these comments; and when data are also considered on mean numbers or live pups/litter. Cheminova believes the NOEL for adult toxicity is 5 ppm (0.34 mg/kg bw/day male; 0.41 mg/kg bw/day female), based on body weight loss during lactation at 25 ppm. Decreased body weight gain in pups was seen at the same 25 ppm dose, and there was an equivocal decrease in pup survival (25 ppm is an NOEL or is very close to one for this effect). The NOEL for pup toxicity is 5 ppm (0.34 mg/kg bw/day male, 0.41 mg/kg bw/day female), based on adult food consumption).

Löser and Eiben, 1982 (no MRID)
Test Material: 95.0% Purity
Dose Levels: 2.0, 10.0, 50.0 ppm

This study is summarized in Attachment B (copy included with this submission). It has numerous deficiencies and is incompletely reported. However, it casts some light on the pup survival issue. The high dose tested in this study was 50 ppm (2-3 mg/kg bw/day, based on adult compound consumption in other dietary studies; the intake of young during late lactation would be significantly higher). This dose was frankly toxic to adults (based on decreased weight gain; ChE was not evaluated in this study nor were clinical signs reported). The high dose caused marked decreases in pup survival. No data were available to determine the cause of pup

death, that is, direct toxicity to pups or a failure to nurture. At 10 ppm (approximately 0.6 mg/kg bw/day based on other dietary studies), no decreased pup survival was found when pup survival was analyzed on a per litter basis. (Statistical reanalyses of pup survival on a per litter basis shown in Attachment B.)

Together, the results of these studies show the NOEL for effects on pup survival is between 10-25 ppm, and probably close to 25 ppm. Effects on adults and pups (decreased weight gain) were seen at 25 ppm, with a NOEL set in the Guideline reproductive toxicity study at 5 ppm (0.34 mg/kg bw/day male, 0.41 mg/kg bw/day female, based on adult compound consumption; compound consumption on a mg/kg bw/day basis for pups during late lactation would be significantly higher). For comparison, based on other subchronic rat toxicity data, the NOEL for RBC cholinesterase inhibition is approximately 0.1 mg/kg bw/day.

F. MUTAGENICITY

Cheminova concurs with EPA's conclusions regarding the results of the various mutagenicity studies. Further mutagenicity studies are unlikely to provide useful information, given that adequate oncogenicity studies in two species showed no oncogenic potential for methyl parathion.

G. METABOLISM

Cheminova has no comments on the metabolism summary.

H. NEUROTOXICITY

1. Acute neurotoxicity study in rats

Minnema, 1994a; (MRID 43254401)
Test Material: 93.1% Purity
Dose Levels: 0.025, 7.5, 10.0 (male), 15.0 (female) mg/kg bw

Cheminova concurs with EPA that the NOEL for neurotoxicity in this study is 0.025 mg/kg, based on clinical findings and brain cholinesterase inhibition at 7.5 mg/kg. It should be noted, as discussed in Attachment B, that this guideline study was designed as a screen for neurotoxicity (not to provide a NOEL for any endpoint for risk calculations). Very high and toxic doses were intentionally administered in accordance with the Guideline, far exceeding any conceivable dietary intake. The mid (7.5 mg/kg) and high (10 mg/kg and 15 mg/kg for males and females, respectively) dose levels in the methyl parathion acute neurotoxicity study actually exceed the value cited by EPA as the LD_{50} for an oral acute dose of methyl parathion.

Neuropathological evaluation showed an increased incidence of myelin lesions in the high-dose males and females, and a marginal, possibly treatment-related effect in the males at 7.5 mg/kg bw. No treatment-related findings were seen in males at 0.025 mg/kg. Females at 0.025 mg/kg were not evaluated because of the absence of treatment-related findings in females at 7.5 mg/kg. Findings are summarized in Table 5 in Attachment B. The high-dose rats show an increased incidence of demyelination, compared to the incidence in the control animals. The lesion was also observed in control animals and was the same histomorphologically in the control and dosed groups. There was a minor increase in severity of this finding (from minimal to slight) in the high-dose group compared to the controls. Mid dose (7.5 mg/kg) females did not show an increased incidence for this finding; in contrast, no mid dose females were affected. The response seen in the mid dose males is considered marginally treatment-related based on several factors:

- Relatively few nerve fibers were affected.

- There was no increase in severity of the lesion in the mid dose group compared to controls (the lesions were considered minimal in severity in both groups).

- The incidence and distribution of the lesions was even less than that observed in the female control group.

Therefore, Cheminova believes that the NOEL for neuropathology in this study is 7.5 mg/kg for females and is very close (or equal) to 7.5 mg/kg in males.

2. Subchronic neurotoxicity study in rats

Minnema, 1994b; (MRID 43490501)
Test Material: 93.1% Purity
Dose Levels: 0.5, 5.0, 50.0 ppm

Cheminova concurs with EPA that neurotoxicity was evident in this study at 50 ppm (3.12 or 4.05 mg/kg bw/day), based on clinical signs, behavioral changes, and brain cholinesterase inhibition, with an NOEL of 5 ppm (0.31 or 0.37 mg/kg bw/day in males and females, respectively). RBC cholinesterase was inhibited at 5 ppm (a 25% to 27% decrease compared to control). Because the degree of RBC inhibition at 5 ppm was relatively slight, and there was no evidence of brain cholinesterase inhibition, clinical signs of toxicity, or neurobehavioral effects in a rigorous evaluation, Cheminova concludes that the low effect level (LEL) for RBC cholinesterase inhibition in this study is $\leq$ 5 ppm ($\leq$ approximately 0.3 mg/kg bw/day), but very close to that dose level. Cheminova concurs with the EPA reviewer that the NOEL for

neuropathological findings was 50 ppm (HDT). It is unclear why the Toxicology Chapter contradicts itself on page 17 by stating that "the incidences of degenerative lesions of peripheral nerves at 50 ppm . . . were equivocal"; this appears to be a misstatement on EPA's part that should be corrected.

(Note: Mean compound intake values were calculated by Cheminova, as follows)

ppm	mg/kg bw/day	
	Male	Female
0.5	0.03	0.04
5.0	0.31	0.37
50.0	3.12	4.05

These values differ slightly from those calculated by the EPA reviewer. Data used for these compound consumption calculations are shown in Attachment B.)

3. Chronic neurotoxicity study in rats

Daly, 1991 (MRID 41853801)
Test Material: 94.6% Purity
Dose Levels: 0.5, 2.5, 12.5, 50.0 ppm

Cheminova concurs that no ocular effects were seen at any dose level in this one-year study. Cheminova also concurs with EPA that neurotoxicity was present at 50 ppm, based on clinical signs of toxicity and decreased brain and RBC cholinesterase activity. The NOEL for cholinesterase inhibition in this study is 2.5 ppm (0.11 mg/kg bw/day). Cheminova, however, does not concur with EPA's conclusions regarding treatment-related neuropathological effects. The EPA review does not include a discussion of the recent reevaluation of sciatic and tibial nerve tissues from the 12-month methyl parathion rat study (Brennecke, 1996; MRID 44204501).

The original study pathologist concluded that effects on the sciatic nerve were present at doses $\geq$ 2.5 ppm, with increased severity of findings at 50 ppm. The original EPA review concluded, based on the data from evaluation of perfused rats provided by the EPL pathologist, that the NOEL for peripheral nerve lesions was 2.5 ppm. Statistical significance of findings was assessed by the EPA reviewer by combining data from males and females. However, there are biological reasons why this should not be done for sciatic nerve evaluations (chronic housing on wire mesh bedding may damage the sciatic nerve; males are more susceptible to this damage because of their higher body weight).

As discussed in Attachment B, at the request of EPA, Cheminova undertook a peer review of peripheral nerve tissue slides from the 1-year study to assist EPA in making a decision regarding an NOEL for neurotoxicity. Certain limitations in the available data precluded a full "peer review" evaluation; however, prior to the reevaluation, EPA agreed to the procedures to be used in the neuropathological re-evaluation.

The reevaluation of nerve tissue included more animals per dose group and was standardized as far as possible for number and quality of the nerve tissue sections evaluated for each animal. The results failed to show any treatment-related effect on peripheral nerves (Re-evaluation of sciatic and tibial nerve tissues; Brennecke, 1996, MRID 4420450).

EPA did not transmit the EPA DER (OPP, 1997) of the reevaluation of peripheral nerves to Cheminova by EPA until September 30, 1998, although EPA completed the review in September, 1997. This EPA delay precluded any opportunity for Cheminova to develop a comprehensive rebuttal to the concerns expressed by the EPA reviewer. EPA completely dismissed the results of the reevaluation (the original NOEL for neuropathology was retained), and the reevaluation was given no weight in the overall evaluation of neuropathology potentially associated with methyl parathion. (In fact, the existence of the reevaluation is not even mentioned by EPA in either the HID document for methyl parathion or in the Toxicology Chapter.) The dismissal appeared to be based primarily on procedural issues; however, as noted above, Cheminova discussed the procedures to be used in the reevaluation with EPA and obtained EPA's concurrence with these procedures. Further, EPA did not make any attempt to communicate with Cheminova for clarification regarding the procedures used in the reevaluation or to let Cheminova know that the reevaluation was not satisfactory.

In the EPA DER for this reevaluation, EPA concluded that, based on the reevaluation, an NOEL of 12.5 ppm could be found. According to EPA's review, this conclusion is based partially on a highly equivocal increase in sciatic nerve lesions in 13-month males at 50 ppm and partially on findings in teased sural nerve sections (which were not reevaluated). Cheminova disagrees that any treatment-related effect was evident in the re-evaluation, for reasons detailed in Attachment B. Cheminova also believes that the validity of the methods used in the teased nerve preparations is questionable; these methods are no longer typically used because of the high variability in the findings.

The results of the Brennecke reevaluation of peripheral nerve tissues in the 1-year rat study cast significant doubt as to whether treatment-related neuropathological effects were present in the low or mid dose of the 2-year chronic study. The 12-month study findings show that the chronic study

findings might not be replicated if the chronic study had included evaluation of more animals, and (possibly) if the original chronic study evaluation had included a more standardized selection of nerve sections for evaluation. The absence of treatment-relationship of these findings in the 1-year study is also supported by the absence of treatment-related neuropathological lesions in the subchronic neurotoxicity study, which tested the same high dose of 50 ppm. The latter study included evaluation of longitudinal and cross sections from perfused animals in the dose groups and, as discussed above, showed no treatment-related effects on peripheral nerve tissue.

Also supporting the conclusion that neuropathology is not a treatment-related consequence of low-dose methyl parathion exposure is the absence of evidence of neuropathology in the rat two-generation study (Daly and Hogan, 1982). Although not including histopathological evaluations of tissues from perfused animals, this study did include histopathological evaluation of eyes (with optic nerve), brain, and sciatic nerve from F1 adults, and from F1 and F2 weanlings. This study produced no evidence of treatment-related histopathology in nervous system tissues.

There is no indication, however, that EPA conducted a comprehensive weight-of-the-evidence evaluation of the treatment-relationship of neuropathological findings or clarification of the NOEL for these findings, although several EPA memoranda indicate that this should be done. Cheminova would like to discuss with EPA whether and how a comprehensive reevaluation of the neuropathological findings (potentially including a peer review of slides) from the two chronic rat studies and the subchronic rat study should be conducted. Cheminova believes in the interim that EPA should clearly identify the uncertainties regarding treatment-related neuropathology in these studies.

I. DERMAL ABSORPTION

EPA is proposing a default dermal absorption factor of 100%, based on EPA's rejection of a rabbit dermal toxicity study. Cheminova believes this is a significant overestimate of potential dermal penetration. Cheminova is currently developing additional short-term dermal penetration data in rats, which should help address this issue. Cheminova believes that, in the interim, adequate comparative acute oral and dermal data are available to predict that dermal penetration of methyl parathion will be in the range of 10 % to25%. (These data are discussed in Attachment B).

J. REFERENCE DOSE FOR ORAL EXPOSURE

In selection of an endpoint for development of an RfD for chronic dietary exposure, EPA considered only the Daly and Hogan, 1983, chronic (2-year) rat

study, and failed to consider the results of either the subchronic neurotoxicity rat study or the 12-month chronic rat study. As noted previously, the 2-year study has some limitations that should be considered before relying on it for developing an RfD. Among these limitations are that the number of animals evaluated for neuropathological findings in the 2-year chronic rat study is not adequate to define an NOEL for peripheral nerve effects, and that the high incidence of intercurrent infection in this study may have compromised the chronic toxicity evaluation. Further, as discussed in the review of the chronic rat study (III.C.2.), Cheminova does not agree with the NOEL of 0.02 mg/kg bw/day determined by EPA from this study. Cheminova believes that 0.2 mg/kg bw/day is a NOAEL dose in this study.

As discussed previously, EPA memoranda reviewing the chronic rat studies have discussed the need for a peer review for characterization of the NOEL for methyl parathion neurotoxicity. Cheminova agrees this would be appropriate, particularly as a reevaluation of nervous system tissues (Brennecke, 1996) from the 12-month chronic study showed no treatment-related peripheral nerve lesions at any dose. Cheminova would like to discuss with the Agency how such an evaluation could be conducted.

In the interim, Cheminova believes 0.11 mg/kg bw/day derived from the one-year rat chronic study is a reasonable NOAEL for use in deriving an RfD, based on findings in all three of the longer term rat studies. Results of these three studies are summarized in Table B-16 in Attachment B.

Good concordance is shown for the results of these studies for most of the parameters evaluated, and 0.11 mg/kg bw/day from the 1-year rat study is a conservative choice for an NOAEL. This study was selected for NOEL derivation in lieu of the 2-year study because of the inadequate neuropathological evaluations in the 2-year study and because of the high rate of intercurrent infection in the 2- year study, which may have confounded the systemic toxicity evaluation.

That an NOAEL of 0.11 mg/kg bw/day is conservative for intermediate to longer term exposures to methyl parathion is also supported by a human 30-day oral study of methyl parathion, which showed an NOEL of 0.31 mg/kg bw/day for plasma and RBC cholinesterase inhibition (Rider et al., 1971). Although this is an older study with some deficiencies and limited reporting, the study design appears basically sound for evaluating potential effects on cholinesterase in humans. EPA, in fact, used the human study as the basis in setting a drinking water Health Advisory for methyl parathion in 1988 (Office of Drinking Water, 1988). Although Cheminova believes that the available data from this study are too limited to use exclusively as a basis for risk assessment, the study results provide assurance that the animal study results are not under-predicting toxicity to humans.

Additionally, for the reasons detailed in this document and in Attachment B, Cheminova does not believe that retention of the FQPA 10X safety factor is appropriate for methyl parathion.

IV. TOXICITY ENDPOINT SELECTION

Cheminova believes that endpoint selection in the Toxicology Chapter document for methyl parathion is overly conservative and fails to adequately consider the impact of the exposure route, high dose to low dose extrapolation, and the likely dermal absorption of methyl parathion.

A. ACUTE DIETARY EXPOSURE

EPA is proposing use of the NOEL from the gavage acute neurotoxicity study for endpoint selection for acute dietary exposure situations.

Cheminova is currently conducting an acute dietary neurotoxicity evaluation of methyl parathion in rats to better characterize the NOEL for acute oral exposure. This study will include neuropathological evaluations.

As discussed in Attachment B, choosing the NOEL from the acute gavage neurotoxicity study for estimation of acute dietary risk is overly conservative because of the dose selection imposed by the study objective to characterize neurotoxic potential at high doses.

EPA's Toxicology Endpoint Selection Process Guidance (Rowland, 1997) provides:

> A dose should not be selected routinely [as the NOEL] by default simply because it is the NOEL. The entire dose response curve should be reviewed to determine how the NOEL relates to the dose at which effects actually begin to appear (i.e., the LOEL). In some cases, data from two studies may be considered together to determine the most appropriate NOEL.

Because the endpoint of concern is neuropathological changes, which would not be expected to be reversible, the subchronic study provides useful data to use in conjunction with the acute study to determine the NOEL for neuropathology.

As previously noted, the data from this subchronic study provide support for a hypothesis that an acute dietary dose of 0.3 mg/kg would not be anticipated to show any adverse clinical signs or significant inhibition of RBC or brain cholinesterase, and that up to 10-fold greater acute dietary exposures would not be

likely to lead to any adverse irreversible neurobehavioral effects or neuropathological findings.

Cheminova recommends that the subchronic neurotoxicity data be taken into consideration for establishing a NOAEL for acute dietary exposure, and that 0.3 mg/kg be used as a surrogate NOEL for acute dietary risk calculation until the additional acute study is completed.

Additionally, for the reasons detailed in this document and in Appendix A, Cheminova does not believe that retention of the FQPA 10X safety factor is appropriate for methyl parathion.

B. SHORT-TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE

EPA is proposing use of the NOEL from the gavage acute neurotoxicity study for endpoint selection for short-term exposure situations.

Cheminova is currently conducting a short-term (5-day) dermal study in rats to better characterize the NOEL for neurotoxicity following exposure by this route. This study will include neuropathological evaluations.

Cheminova recommends that in the interim, the subchronic neurotoxicity study be selected for use in short-term occupational risk assessment. This study showed an NOEL for neurobehavioral effects and for inhibition of brain cholinesterase at 5 ppm (approximately 0.3 mg/kg bw/day) and an NOEL for neuropathological findings at 50 ppm (HDT). RBC cholinesterase inhibition was seen at the 0.3 mg/kg bw/day dose level; however, Cheminova believes that this dose level is extremely close to an NOAEL for subchronic exposure to methyl parathion. This conclusion is supported by the absence at 0.3 mg/kg bw/day of behavioral effects or clinical signs of toxicity, which were evaluated in this study much more rigorously and systematically than in a standard subchronic study. Cheminova considers this dose level an LEL, however an appropriate conservative extrapolation would set the NOEL using a 3-fold factor, that is, to 0.1 mg/kg bw/day.

It should be noted that EPA states in the cover letter to the Toxicology Chapter that the additional FQPA 10X safety factor would not be retained for occupational exposures. Cheminova agrees with this policy decision by EPA regarding occupational exposures, although Cheminova does not agree that the 10X factor should be retained for any risk calculation for methyl parathion, as discussed above. EPA should correct the Toxicology Chapter and delete the indication on page 20, section 3 of the Toxicology Chapter that “a UF of 1000 will be used, which includes an additional UF of 10, for the protection of infants and children.”

As noted above, the short-term exposures are occupational, because there are no registered residential uses for methyl parathion.

C. INTERMEDIATE-TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 WEEK TO SEVERAL MONTHS)

EPA is proposing use of the Daly and Hogan, 1983 rat two-year chronic study for this endpoint. The subchronic neurotoxicity study (Minnema, 1994) provides a time frame that is more relevant to intermediate-term occupational exposure to methyl parathion (as indicated above, residential exposure is precluded) than does the chronic feeding study. The subchronic study also included specific test parameters to more completely characterize neurotoxicity and more detailed neuropathological evaluations than did the chronic study.

Therefore, Cheminova recommends that the subchronic neurotoxicity study results be used to assess the potential risks from intermediate-term exposure with NOEL determination as discussed above under short term exposure.

That an NOEL of 0.1 mg/kg bw/day is conservative for intermediate to longer term exposures to methyl parathion is also supported by a human 30-day oral study of methyl parathion, which showed an NOEL of 0.31 mg/kg bw/day for plasma and RBC cholinesterase inhibition (Rider et al., 1971). For reasons provided earlier, Cheminova believes the available data from this study are too limited to be used exclusively as a basis for risk assessment. However, the human study results provide assurance that the animal study results are not under-predicting toxicity to humans.

Again, Cheminova agrees with the EPA's decision not to retain the additional FQPA 10X safety factor for intermediate-term occupational exposures; although as discussed previously, Cheminova does not believe there is a substantive basis for retaining this factor for any risk scenarios.

EPA should correct the Toxicology Chapter and delete the indication on page 20, section 4 that “a UF [uncertainty factor] of 1000 will be used, which includes an additional UF of 10, for the protection of infants and children.” As noted above, the intermediate-term exposures are occupational, because there are no registered residential uses for methyl parathion.

D. CHRONIC OCCUPATIONAL OR RESIDENTIAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)

Cheminova believes, for the reasons discussed in Section III. J. in this document, that the Daly and Hogan, 1983 two-year chronic rat study should not be used as the sole basis for assessing the risk of chronic exposure to methyl parathion.

Cheminova believes that an NOAEL derived from evaluation of all three of the longer term rat studies provides a conservative endpoint for risk assessment. The conservatism of this selection is supported by the findings in a subchronic human study, as discussed above.

Again, Cheminova agrees with EPA's decision not to retain the additional FQPA 10X safety factor for intermediate-term occupational exposures; although as discussed previously, Cheminova does not believe there is a substantive basis for retaining this factor for any risk scenario.

E. INHALATION EXPOSURE (FOR ALL ABOVE SCENARIOS)

EPA has concluded that the NOEL from the Daly and Hogan, 1983 two-year rat chronic study should be used for all inhalation exposure scenarios.

Cheminova has several concerns regarding EPA's conclusions in this area.

First, it is not appropriate to select an NOEL from a chronic study as the basis for risk assessment for acute and intermediate exposures as well as for long-term exposures. Endpoints from studies of the appropriate duration should be selected for each different exposure scenario.

Second, both occupational and ambient exposures to methyl parathion may be reasonably expected to be seasonal, with occasional acute peaks, rather than chronic. This contention is supported by the seasonal, sporadic use patterns for methyl parathion, the absence of residential uses, and the rapid degradation of methyl parathion in air. Cheminova suggests that either the 3-month neurotoxicity study (NOEL of 0.1 mg/kg bw/day) or the one-year chronic rat study (NOEL of 0.11 mg/kg bw/day) would provide more correct choices for risk assessment (depending on the duration of the exposure in question).

Third, to reiterate, EPA states in the cover letter to the Toxicology Chapter that the additional FQPA 10X safety factor would not be retained for occupational exposures. [Cheminova agrees with this policy decision by EPA regarding occupational exposures, although Cheminova does not agree that the 10X factor should be retained for any risk calculation for methyl parathion, as discussed above.]

EPA should differentiate in this section between occupational exposures and exposures to the general population, and appropriately modify the indication on page 21, section 5 that "a UF of 1000 will be used, which includes an additional UF of 10, for the protection of infants and children."

Attachment B

Comments on EPA's memorandum titled "Methyl Parathion: Hazard Identification Committee Report"

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66 pages

TABLE OF CONTENTS

I. INTRODUCTION

This Attachment provides Cheminova Agro A/S's (Cheminova's) comments on the "EPA Health Effects Division (HED) - Hazard Identification Committee's (HID) Evaluation of Methyl Parathion" (December 1, 1997). Cheminova disagrees with EPA's conclusion that the Food Quality Protection Act (FQPA) additional safety factor should be retained for methyl parathion. Cheminova also disagrees with EPA's characterization of toxicity in several key toxicology studies, and with EPA's conclusions on toxicity study end-point selection. The bases for Cheminova's position are summarized in the methyl parathion overview document.

Cheminova concurs with EPA's conclusion that methyl parathion has been adequately tested for oncogenic effects in two species and that the data show that methyl parathion is not likely to be carcinogenic in humans (Category E). Cheminova also concurs with EPA that further mutagenicity testing is unlikely to provide useful information, particularly in light of the negative oncogenicity classification. Because Cheminova agrees with EPA on these matters, these conclusions are not discussed further in this document.

This attachment first reviews the developmental and reproductive toxicity studies discussed in EPA's HID document that were conducted in accordance with EPA's 40 Code of Federal Regulations (CFR) Part 158, Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Study Guidelines, and the Good Laboratory Practice (GLP) requirements, and submitted to EPA by Cheminova or other registrants. This attachment also discusses a second Supplementary rat developmental toxicity study, a second Guideline rabbit developmental toxicity study, and a Supplementary rat reproductive toxicity study, which were not included in the HID review.

Second, this attachment critically reviews the published journal-article references relating to the developmental toxicity of methyl parathion after *in utero* exposure, or following direct exposure to pups, that form the primary basis for EPA's conclusions about both the need for a developmental neurotoxicity study and for retention of the 10X safety factor. We also discuss other relevant published studies.

Third, this attachment addresses acute neurotoxicity issues. Because it is important to evaluate the neuropathological findings in the acute neurotoxicity study in the context of findings in other studies, the attachment discusses the results of the subchronic neurotoxicity study, the rat 2-year chronic study, and the rat 12-month chronic study with special evaluations of eyes and peripheral nerves.

Finally, this attachment comments on EPA's study selection for acute, short-term, intermediate, and chronic risk assessment; on EPA's study selection inhalation risk assessment; and on EPA's 100% default factor used for dermal absorption.

II. DEVELOPMENTAL AND REPRODUCTIVE TOXICITY

A. DEVELOPMENTAL TOXICITY

Extensive GLP-compliant studies have been conducted to evaluate the potential developmental toxicity of methyl parathion. The required core studies in rats and rabbits have been conducted and the Agency has found them acceptable. Cheminova concurs with EPA that these studies do not show unique fetal susceptibility to methyl parathion. These data provide the most reliable basis for evaluating the potential for susceptibility of fetuses to *in utero* exposure to methyl parathion. Therefore, the results of these core studies should be given the most weight in evaluating whether there is credible evidence of increased fetal susceptibility to this compound.

1. Developmental Toxicity Studies (Guideline 83-3) Reviewed by EPA in the HID Document

Becker et al., 1987; and Becker, 1991 (MRID 41136101, MRID 42235601): A developmental toxicity study was conducted in Wistar rats at doses of 0.3, 1.0, or 3.0 mg/kg bw/day administered by gavage on gestation days (GD) 6 through 15. The vehicle was 1% aqueous Cremophor EL emulsion, at a constant dose volume of 10 mL/kg. Dams were monitored for clinical signs and body weight effects; plasma, red blood cell (RBC), and brain cholinesterase (ChE) were evaluated from satellite animals in the control and high-dose groups. These measurements were done pretest (except for brain ChE) and at termination of the satellite group animals on GD 16. Main study dams were necropsied after termination on GD 21, and the number of corpora lutea was recorded. Fetuses were examined for external (all), visceral (half), and skeletal malformations (half). The following data were collected: number of implantations; number of early and late resorptions; number of live and dead fetuses/group; fetal body weight; sex ratio of fetuses; and external, visceral, or skeletal anomalies.

Severe maternal toxicity was evident at 3.0 mg/kg bw/day, including increased mortality; clinical signs (somnolence, ataxia, dyspnea, recumbency, and chewing behavior); and decreased body weight, body weight gain, and food consumption. The NOEL for these findings was 1.0 mg/kg bw/day. Plasma, RBC, and brain ChE inhibition were also seen in the 3.0 mg/kg bw/day dams; these parameters were evaluated in high-dose and control dams only.

Developmental effects included decreased fetal body weight and increased incidence of delayed ossification at 3.0 mg/kg bw/day only. There was also an increase in post-implantation loss (all early resorptions), a change that was due to the severe maternal toxicity seen at the 3.0 mg/kg bw/day dose according to the study authors. The treatment relationship of the increase in post-implantation loss is equivocal, however, for the following reasons: no statistical significance was achieved relative to control, there was no clear evidence of a dose response, the mean number of fetuses per dam was virtually the same between the control and high-dose dams (12.9 and 12.5, respectively), and there was no increase in late resorptions or in the number of dead fetuses. The NOEL for developmental toxicity was 1.0 mg/kg bw/day. The study showed no evidence of teratogenicity, or evidence of increased fetal susceptibility following maternal exposure to methyl parathion. This study was considered to be core minimum by EPA following submission of additional data showing the correlation between fetal body weight and delayed ossification.

Renhof, 1984 (**Accession Nos. 00259403, 00259404, 00259405**); **and Renhof, 1987a and b (MRID Nos. 41199001 and 41046101)**: In a developmental toxicity study conducted in pregnant Himalayan rabbits (15/dose), methyl parathion was administered by gavage at doses of 0, 0.3, 1.0, and 3.0 mg/kg bw/day. The vehicle was 0.5% aqueous Cremophor at a dose volume of 5 mL/kg. Does were monitored for clinical signs and body weight effects. This study did not evaluate ChE, but a supplementary study described below did. Fetuses were examined for external, visceral, and skeletal malformations. The following data were collected: number of implantations; number of live or dead fetuses; sex of fetuses; average placental weight and fetal body weight (litter weight and mean fetal weight/litter); and external, visceral, and skeletal malformations. The number of early and late resorptions was reported in a supplementary submission.

Supplementary data were submitted to support the dose selection for this study. Five inseminated Himalayan rabbits/group were administered methyl parathion by gavage at doses of 0, 0.3, 1.0, and 3.0 mg/kg bw/day during GD 6 through 18. Plasma and erythrocyte ChE activities were assessed prior to the first, second, and ninth days of dosing, and at 24 hours after the final dose. Brain ChE activity was also measured 24 hours after the final dose on GD 19. In this supplementary study, no clinical signs or treatment-related effects on body weights were seen at any dose level. The study report concludes that plasma and RBC ChE were inhibited at all dose levels; this inhibition was marked (39% and 30% for plasma and RBC ChE, respectively) in the 3.0 mg/kg bw/day group. Brain ChE was not inhibited in the treated animals compared to the controls at any dose level. With the exception of brain ChE, however, the author's conclusions are based on comparison to pretest values

and not on comparison to the concurrent control values. Comparison to the concurrent control values shows statistically significant inhibition of RBC ChE only at the final two assessments of the 3.0 mg/kg bw/day high-dose group. Compared to concurrent controls, there is no evidence of an effect on RBC ChE at 0.3 or 1.0 mg/kg bw/day and no statistically significant inhibition of plasma ChE. Therefore, the NOEL for brain ChE inhibition in this supplementary study in Himalayan rabbits was 3.0 mg/kg bw/day, and the NOEL for RBC cholinesterase inhibition was 1.0 mg/kg bw/day.

The definitive rabbit developmental toxicity study revealed no treatment-related clinical observations or effects on body weight or weight gain of the does. It showed no dose-related effects on the number of live fetuses per litter, the number of early or late resorptions per litter, mean fetal or placental weight, number of fetuses with skeletal alterations per litter, number of runt fetuses per litter, or number of fetuses with malformations. The maternal and developmental NOEL in this study was 3.0 mg/kg bw/day (highest dose tested (HDT)).

This study has some deficiencies, although most of the data deficiencies and the justification for dose selection have been addressed in the report supplements. Individual fetal findings are not presented. No homogeneity or dose concentration analyses were done, although separation of test material in suspension for the high dose was noted after 24 hours (the high dose was mixed daily). However, the study was considered acceptable by EPA following receipt of the supplementary data (including the data on ChE inhibition), and the results show no fetal susceptibility to methyl parathion in rabbits exposed to up to 3.0 mg/kg bw/day.

2. Developmental Toxicity Studies (Guideline 83-3) Not Reviewed by EPA in the HID Document

In conducting a weight-of-the-evidence evaluation, all available data should be considered, and the analysis should discount or give less weight to particular studies based on concerns regarding validity, poor experimental design, or poor reporting. One supplementary older study of rat developmental toxicity (Machemer, 1977, MRID 00143747), however, was not included in the EPA assessment of the potential developmental toxicity of methyl parathion summarized in the HID review. A summary of this study follows.

Further, a recent Guideline developmental toxicity study in rabbits (Hoberman, 1991) was conducted with methyl parathion to fulfill a California Department of Pesticide Registration data requirement. This study, summarized below, further demonstrates the absence of unique developmental toxicity following *in utero* exposure to methyl parathion. A copy is included with this submission.

Machemer, 1977 (MRID 00143747): In a rat developmental toxicity study, methyl parathion was dosed by gavage to 20-24 fertilized Wistar females/group at doses of 0, 0.1, 0.3, and 1.0 mg/kg bw/day on GD 6 through 15. The vehicle was 1% aqueous Cremophor EL emulsion, at a constant dose volume of 10 mL/kg. Dams were monitored for clinical signs and body weight effects; ChE was not evaluated. Fetuses were examined for external (all), visceral (one-third), and skeletal malformations (two-thirds). The following data were collected: number of implantations, number of fetuses/group, number of dead and resorbed fetuses, average placental weight and fetal body weight, frequency of fetuses with retardation of bone development, sex ratio of fetuses, and malformations.

Dams showed statistically significant decreased weight gain during gestation at 1.0 mg/kg bw/day. The maternal toxicity at 1.0 mg/kg bw/day was associated with a decrease in fetal body weight (including an increased incidence of "stunted" fetuses weighing < 3 grams). There was no treatment-related effect on number of implantations, number of fetuses/group, number of dead and resorbed fetuses, average placental weight, frequency of fetuses with retardation of bone development, sex ratio of fetuses, or malformations. No maternal or developmental toxicity was evident at 0.3 mg/kg bw/day.

This study has several deficiencies (no maternal food consumption, necropsy, or cholinesterase data; no individual fetal data or description of skeletal variations; and a failure to analyze the fetal data on a per litter basis). However, the study evaluated an adequate number of litters, the high dose produced clear maternal toxicity showing adequate dose selection, the route of administration was the recommended route to assess the impact of oral exposures, and the exposure duration corresponds with current guidelines. Therefore, this study provides additional support for the conclusion that there is no unique fetal susceptibility to methyl parathion.

Hoberman, 1991: In this developmental toxicity study in New Zealand White rabbits, methyl parathion was administered by gavage on GD 6 through 18 at doses of 0, 0.3, 3.0, and 9.0 mg/kg bw/day. A corn oil vehicle was used, at a dose volume of 1.0 mL/kg/day. Dose selection was based on a range-finding study that showed treatment-related mortality in doses at 12 and 15 mg/kg and clinical signs of toxicity in doses at 9 mg/kg bw/day. In the definitive study, does were monitored for clinical signs, body weight, and food consumption; plasma and RBC ChE were evaluated following dosing on GD 18. Does were necropsied on GD 21, and the number of corpora lutea (CL) was recorded. All fetuses were examined for external, visceral, and skeletal malformations. The following data were collected: number of implantations; number of early and

late resorptions; number of live and dead fetuses/group; fetal body weight; sex ratio of fetuses; and external, visceral, or skeletal alterations.

There was no treatment-related mortality. Three abortions occurred in the study, one each in the control and 1.0 and 3.0 mg/kg bw/day dose groups. There were no treatment-related clinical signs of toxicity or findings at gross necropsy at doses up to 9.0 mg/kg bw/day HDT. (In contrast, in the range-finding study in pregnant rabbits, the 9.0 mg/kg bw/day dose caused tremors, ataxia, excess salivation, and gasping.) Maternal body weight and food consumption were not affected, and plasma ChE was inhibited only in the high-dose group. RBC ChE, assessed after dosing on GD 18, was statistically significantly inhibited compared to control in all dose groups. RBC ChE inhibition in the 0.3 mg/kg bw/day dose group, however, while statistically decreased compared to control, was less than 20% decreased, and no clinical signs of toxicity were observed. Thus, this dose level is considered a maternal NOEL.

There was no effect on pregnancy indices, and the litter averages for number of corpora lutea, number of implantations, number of early and late resorptions, litter sizes, and live fetuses were comparable among all groups. The litter averages for percent male fetuses and fetal body weights were similar in all groups. There were no treatment-related increases in the fetal or litter incidences of external, visceral, or skeletal alterations. The NOEL for developmental toxicity in this study was 9.0 mg/kg bw/day (HDT).

This study was a guideline developmental toxicity study (Guideline 83-3) that was considered Acceptable by California reviewers. This study also provides a rabbit developmental toxicity study conducted at higher dose levels. Thus, it should be given significant weight in the evaluation of potential fetal susceptibility to methyl parathion.

3. Conclusion

In conclusion, both rat and rabbit Guideline developmental toxicity studies fail to provide evidence of unique fetal susceptibility. They also showed no evidence of teratogenicity. Embryotoxicity and/or developmental delay were seen at maternally toxic doses in rats, but not in rabbits.

REPRODUCTIVE TOXICITY (Guideline 83-4)

1. Study Evaluated by EPA

Daly and Hogan, 1982 (MRID 00119087): In a two-generation rat reproductive toxicity study, Sprague-Dawley rats were dosed with methyl parathion in the diet at doses of 0, 0.5, 5.0, and 25.0 ppm. Based on pre-mating

food consumption, compound intake averaged 0, 0.036, 0.34, and 1.73 mg/kg bw/day in F_0 males, and 0, 0.044, 0.41, and 2.1 mg/kg bw/day in F_0 females.

F_0 parents (15 male and 30 female/dose group) were dosed for 14 weeks pre-mating and during mating, gestation, and lactation. Mating was 2 females to 1 male, with a 15-day mating period. Selected F_1 parents (15 male and 30 female/dose group) were subsequently dosed for 15 weeks pre-mating and during mating, gestation, and lactation. Mating procedures were similar to the F_0 animals; sibling matings were not avoided. Adult animals were weighed weekly during pretest, and females on GD 0, 6, 15, and 20, and on lactation days 0, 4, 14, and 21. Food consumption was measured pretest only. ChE was not evaluated in either adults or pups. Necropsies were done on all adults, on all F_1 weanlings not selected to be parent animals, and on all F_2 weanlings. Histopathological evaluations of tissues including male and female reproductive organs, adrenal, brain, eye, heart, intestine, kidneys, liver, lung, lymph nodes, mammary gland, sciatic nerve, pituitary, salivary gland, spleen, stomach, thymus, and thyroid were done on F_1 adults (10/sex/dose), and F_1 and F_2 weanlings (5/sex/dose).

In the F_0-F_1 generation, there were no treatment-related mortalities, or effects on body weight or food consumption on F_0 adults during the pre-mating period. There were no effects on mating or fertility. There were no effects on body weight gain during gestation; high-dose females showed weight loss compared to control females during lactation. There were no treatment-related effects on length of gestation period, number of pups, pup viability, or survival. F_1 pup viability indices calculated on a per litter basis are shown in Table B-1 below. F_1 pup weights were slightly decreased (approximately 10%) in the high-dose group compared to control (not statistically significant). There were no treatment-related findings at necropsy of F_0 adults or of F_1 weanlings, or treatment-related microscopic findings in the F_1 weanlings evaluated.

In the F_1-F_2 generation, there were no treatment-related mortalities or effects on food consumption of F_1 adults during the pre-mating period. High-dose F_1 females showed persistence of the body weight deficit apparent at weaning; body weight gains in all dose groups were comparable. There were no effects on mating or fertility. There were no effects on body weight gain during gestation; high-dose females showed weight loss compared to control females during lactation.

There were no treatment-related effects on length of gestation period, number of pups born, pup body weight at birth, or litter survival. Table B-2 shows the total number of pups (summed across litters) surviving between days 0 to 4 was slightly but statistically significantly reduced in the high-dose group (97.9% versus 88.5% survival for the control and high-dose F_2 pups, respectively). Pup

survival analyzed on a per litter basis, which is considered most appropriate for survival analyses (as discussed in EPA guidance for reproductive toxicity risk assessment), was slightly affected at the high dose (statistical significance marginal), as shown in Table B-2. However, excluding litters with two or fewer pups born alive (resulting in exclusion of a single high-dose litter), which typically show poorer survival than larger litters, no statistically significant change in viability is seen (Table B-3). (Litter-based survival analysis was conducted by Cheminova.) Further, the mean number of live pups per litter was not affected at any point during lactation (Table B-4). Therefore, the decrease in viability between days 0 to 4 at 25 ppm is not considered likely to be treatment related, or at worst represents a low effect level (LEL) for this effect. Decreased weight gain was seen in the high-dose pups between days 4 to 21; the resulting difference in body weight was not statistically significantly different from control. There were no treatment-related findings at necropsy or following microscopic evaluation of F_1 adults or F_2 weanlings.

Table B-1. Mean and Standard Deviation of the Viability Indices in the First Generation of the Two-Generation Rat Study

Dose Group	Pups Alive on Day 4 as a Percentage of Pups Born Alive		Pups Alive on Day 21 as a Percentage of Pups Born Alive		Pups Alive on Day 21 as a Percentage of Pups Alive on Day 4	
Control	98.51%	(3.39%)	98.51%	(3.39%)	100.0%	(0.00%)
0.5 ppm	97.25%	(7.59%)	96.17%	(8.30%)	98.92%	(4.17%)
5.0 ppm	99.27%	(2.36%)	99.27%	(2.36%)	100.0%	(0.00%)
25.0 ppm	99.22%	(2.72%)	98.16%	(5.00%)	98.88%	(3.20%)

Table B-2. Mean and Standard Deviation of the Viability Indices in the Second Generation of the Two-Generation Rat Study When All Litters Are Included

Dose Group	Pups Alive on Day 4 as a Percentage of Pups Born Alive		Pups Alive on Day 21 as a Percentage of Pups Born Alive		Pups Alive on Day 21 as a Percentage of Pups Alive on Day 4	
Control	97.92%	(4.77%)	96.84%	(5.69%)	98.89%	(2.88%)
0.5 ppm	96.94%	(10.35%)	94.05%	(20.36%)	95.02%	(20.43%)
5.0 ppm	98.25%	(4.27%)	96.03%	(8.53%)	97.78%	(7.92%)
25.0 ppm	88.52%*	(25.16%)	87.77%	(25.46%)	99.07%	(3.93%)

* $p \leq 0.05$

Table B-3. Mean and Standard Deviation of the Viability Indices in the Second Generation of the Two-Generation Rat Study When Litters With Two or Fewer Pups Born Alive Are Excluded

Dose Group	Pups Alive on Day 4 as a Percentage of Pups Born Alive		Pups Alive on Day 21 as a Percentage of Pups Born Alive		Pups Alive on Day 21 as a Percentage of Pups Alive on Day 4	
Control	97.82%	(4.86%)	96.69%	(5.78%)	98.83%	(2.94%)
0.5 ppm	98.99%	(2.74%)	98.14%	(3.71%)	99.15%	(2.83%)
5.0 ppm	98.15%	(4.38%)	97.76%	(4.50%)	99.61%	(1.62%)
25.0 ppm	93.44%	(13.55%)	92.64%	(14.42%)	99.07%	(3.93%)

Table B-4. Methyl Parathion Two-Generation Reproductive Toxicity Study Mean Number of Live F_2 Pups per Litter

Dose Group (ppm)	Mean No. of Live F_2 Pups per Litter (Male and Female)		
	Day 0	Day 4	Day 21
0	12.0 $\pm$ 3.5	11.7 $\pm$ 3.6	11.6 $\pm$3.6
0.5	11.8 $\pm$ 3.4	11.7 $\pm$ 3.4	12.0 $\pm$ 2.7
5.0	12.4 $\pm$ 2.8	12.2 $\pm$ 2.9	12.1$\pm$ 3.0
25.0	11.2 $\pm$ 3.2	11.1$\pm$ 3.0	11.0 $\pm$3.1

The EPA HID document states that there was a treatment-related decrease in pup survival in this study. As discussed above, there were no effects on

survival in F_1 pups, and survival analyses on a per litter basis in conjunction with evaluation of live pups/litter data for F_2 pups do not strongly support the conclusion that there was a treatment-related effect on pup viability. There is evidence of decreased body weight gain in both adults and offspring at the high dose of 25 ppm (1.7 mg/kg bw/day or 2.1 mg/kg bw/day in adult males and females, respectively), with a NOEL of 5 ppm (0.34 mg/kg bw/day or 0.41 mg/kg bw/day in adult males and females, respectively). There is no evidence of increased susceptibility of the pups to methyl parathion.

2. Reproductive Toxicity Study Not Included in the HID Review by EPA

The following reproductive study on methyl parathion conducted by/for a prior registrant was not included in the EPA HID review. Cheminova records do not indicate whether the study had been submitted to EPA previously.

Löser and Eiben, 1982: A three-generation rat reproductive toxicity study tested doses of 2, 10, or 50 ppm methyl parathion in Wistar rats for three generations. This study showed marked increases in pup mortality at 50 ppm (adult doses of approximately 2-3 mg/kg bw/day based on other dietary study data) but not at 10 ppm (approximately 0.6 mg/kg bw/day based on other dietary study data). (Viability analyses were re-done on a per litter basis by the Cheminova reviewer; these are shown in Tables B-5 through B-10). There was also a reduction in the number of live pups at birth at 50 ppm; it is not clear from the reported data if this represents increased post-implantation loss or increased still births.

This study has marked deficiencies, including a lack of information on effects on cholinesterase, clinical signs in adults and pups, or cause of death in pups. Thus, it is not possible to conclude if the pup mortality was due to direct toxicity of methyl parathion to the pups, or to a failure of the dams to nurture their offspring. Graphically presented data in the report show a clear pattern of decreased body weight gain in adults at the high dose (although body weight data for adults were not tabulated or analyzed statistically); as noted previously, the report failed to characterize other effects on adult animals. Based on other rat subchronic and chronic toxicity data, 50 ppm would be expected to severely affect the adult animals.

Table B-5. Mean and Standard Deviation of the Viability Indices in Generation Group F1A of Animals Exposed to Methyl Parathion[1]

Dose Group	Pups Alive on Day 5 (Before Cull) as a Percentage of Pups Born Alive		Pups alive on Day 21 as a Percentage of Pups Born Alive		Pups Alive on Day 21 as a Percentage of Pups Alive on Day 5 (After Cull)	
Control	98.23%	(4.66%)	94.75%	(8.27%)	100.0%	(0.00%)
2 ppm	99.57%	(1.81%)	94.57%	(9.31%)	99.44%	(2.36%)
10 ppm	94.01%	(12.08%)	86.46%	(22.55%)	92.79%	(22.55%)
50 ppm	23.46%	(35.88%)	11.30%	(24.83%)	51.11%	(45.54%)

Table B-6. Mean and Standard Deviation of the Viability Indices in Generation Group F1B of Animals Exposed to Methyl Parathion

Dose Group	Pups Alive on Day 5 (Before Cull) as a Percentage of Pups Born Alive		Pups alive on Day 21 as a Percentage of Pups Born Alive		Pups Alive on Day 21 as a Percentage of Pups Alive on Day 5 (After Cull)	
Control	98.11%	(3.51%)	89.03%	(10.89%)	96.73%	(9.43%)
2 ppm	93.92%	(16.97%)	84.62%	(19.87%)	95.63%	(12.35%)
10 ppm	83.88%	(33.63%)	76.65%	(32.80%)	93.78%	(10.77%)

[1] The study ran Dunnett's test to determine if there is any statistically significant dose-related decrease in animal viability. The test did not detect any statistically significant decrease in pup viability in the first two doses (2 ppm and 10 ppm) of all generations (F1A, F1B, F2A, F2B, F3A, and F3B). Statistically significant decreases in the viability index for animals exposed to 50 ppm were found in the four generations exposed to 50 ppm (F1A, F1B, F2A, F2B). In the analysis of viability, the litters without any pups born alive were excluded from the computations.

Dunnett's test for the generations that included the 50-ppm dose group (F1A, F1B, F2A, F2B) were rerun excluding the highest dose group. That is, the study analyzed generations F1A, F1B, F2A, and F2B comparing only the viability indices in animals exposed to 2 ppm and 10 ppm with the viability indices in the control animals. The reason for this reanalysis is that Dunnett's statistic changes with the number of comparisons and the contribution to the variability of all the groups in the comparison, and statistical differences could be found when the highest drop is excluded. The reanalysis with Dunnett's test applied to the first two dose groups did not detect any statistically significant decrease in the viability indices in animals exposed to 2 ppm and 10 ppm.

50 ppm	28.84%	(39.00%)	13.03%	(30.76%)	33.80%	(42.31%)

Table B-7. Mean and Standard Deviation of the Viability Indices in Generation Group F2A of Animals Exposed to Methyl Parathion

Dose Group	Pups Alive on Day 5 (Before Cull) as a Percentage of Pups Born Alive		Pups alive on Day 21 as a Percentage of Pups Born Alive		Pups Alive on Day 21 as a Percentage of Pups Alive on Day 5 (After Cull)	
Control	94.64%	(13.26%)	85.76%	(13.51%)	100.0%	(0.00%)
2 ppm	99.08%	(2.83%)	91.72%	(9.34%)	99.50%	(2.24%)
10 ppm	96.73%	(6.27%)	84.38%	(22.56%)	93.98%	(22.99%)
50 ppm	19.76%	(31.97%)	9.29%	(21.09%)	35.24%	(44.84%)

Table B-8. Mean and Standard Deviation of the Viability Indices in Generation Group F2B of Animals Exposed to Methyl Parathion

Dose Group	Pups Alive on Day 5 (Before Cull) as a Percentage of Pups Born Alive		Pups alive on Day 21 as a Percentage of Pups Born Alive		Pups Alive on Day 21 as a Percentage of Pups Alive on Day 5 (After Cull)	
Control	98.94%	(3.09%)	87.53%	(11.07%)	90.33%	(3.83%)
2 ppm	86.43%	(28.98%)	72.65%	(35.31%)	86.02%	(28.24%)
10 ppm	87.30%	(23.26%)	73.87%	(25.69%)	87.50%	(25.43%)
50 ppm	0.00%	(0.00%)	0.00%	(0.00%)	No animals alive at day 5	

Table B-9. Mean and Standard Deviation of the Viability Indices in Generation Group F3A of Animals Exposed to Methyl Parathion

Dose Group	Pups Alive on Day 5 (Before Cull) as a Percentage of Pups Born Alive		Pups Alive on Day 21 as a Percentage of Pups Born Alive		Pups Alive on Day 21 as a Percentage of Pups Alive on Day 5 (After Cull)	
Control	93.81%	(16.85%)	72.15%	(29.48%)	80.41%	(30.73%)
2 ppm	99.48%	(2.08%)	93.31%	(8.38%)	97.57%	(6.72%)

10 ppm	94.40%	(11.13%)	89.48%	(15.82%)	96.16%	(9.23%)

Table B-10. Mean and Standard Deviation of the Viability Indices in Generation Group F3B of Animals Exposed to Methyl Parathion

Dose Group	Pups Alive on Day 5 (Before Cull) as a Percentage of Pups Born Alive		Pups Alive on Day 21 as a Percentage of Pups Born Alive		Pups Alive on Day 21 as a Percentage of Pups Alive on Day 5 (After Cull)	
Control	91.88%	(21.83%)	75.41%	(28.19%)	91.88%	(24.82%)
2 ppm	97.94%	(5.28%)	91.05%	(10.38%)	95.55%	(8.27%)
10 ppm	89.22%	(24.99%)	81.65%	(26.10%)	95.83%	(9.24%)

In summary, this three-generation reproductive toxicity study shows no statistically significant decreases in viability indices in animals exposed to 10 ppm of methyl parathion (approximately 0.6 mg/kg bw/day in adult animals). A copy of this study is included with this submission.

3. Conclusion Regarding Reproductive Toxicity Studies

Combined, the data from these reproductive toxicity studies establish a NOEL for pup mortality of $\leq$ 25 ppm (1.73 or 2.1 mg/kg bw/day, males and females, respectively, based on adult data) but at least 10 ppm (approximately 0.06 mg/kg bw/day), and a NOEL for pup body weight effects of 5 ppm (0.34 or 0.41 mg/kg bw/day, males and females, respectively, based on adult data). Neither of the studies provide sufficient data to conclude whether the increased pup mortality at the maternally toxic high dose levels of 25 ppm (equivocal) or 50 ppm (overt) was due to direct toxicity to the pups or a failure to nurture. The NOEL for toxicity to adult rats was 5 ppm (0.34 or 0.41 mg/kg bw/day, males and females, respectively), and no unique susceptibility of the pups to methyl parathion toxicity was evident in either of the studies.

Additionally, based on lack of effects on estrous cyclicity (assessed from time to mating data), mating ability, or fertility in the second and third generations in these studies, prenatal and postnatal exposure to methyl parathion at doses as high as 25 ppm leads to no overt adverse effects on neural or hormonal reproductive development or function.

COMMENTS ON PUBLIC LITERATURE REFERENCES CITED BY EPA

EPA indicates in its review of information in the published literature that "although these studies were not submitted . . . in support of registration, they can be considered in weight-of-the-evidence determinations for methyl parathion." The weight-of-the-evidence evaluation of these published studies must include consideration of the robustness of the data and the validity of the conclusions, as well as an assessment of whether the dosing route and dose levels are relevant to potential human exposures. These issues are critical to adequately evaluate the published studies, which in general show the following: lack of GLP compliance, incomplete data presentations, and in some cases poor study design, irrelevant route of administration, and inappropriate dose selection. At least one study, Gupta et al., 1985, provides an unsubstantiated hypothesis as a conclusion, which has been cited extensively in the HID review and is critical to the HID positions that a developmental neurotoxicity study is needed and that the 10X factor should be applied at this time.

In Utero Exposure: Conventional Developmental Toxicity Studies

Neither published study relating to *in utero* exposure with conventional developmental toxicity endpoints showed any increased susceptibility of the fetuses compared to the dams to toxic effects resulting from methyl parathion exposure.

Fuchs et al., 1976[2]: EPA states that this study showed that methyl parathion administered to pregnant rats in the diet at 3 ppm [sic] resulted in growth retardation and increased incidence of resorptions in the treated group. The HID summary appears to be based on the translated abstract of this German study. There are several inaccuracies in the abstract itself or in the translation of the abstract relied on by EPA. Significantly, methyl parathion was administered orally in this study as a suspension in olive oil at doses up to 3 *mg/kg* bw/day (presumably by gavage) rather than, as stated in the HID document, in the diet at a 3 *ppm* dose level. The intervals of dosing reported in the HID review and in the study abstract are also incorrect. Methyl parathion was reported in the abstract (including the original German abstract) to have been administered from days 5 to 9 and days 11 to 15 or 11 to 19. The published study report, however, states administration was done every 2 days from either days 5 to 15 (dose levels of 0, 0.1, 1, or 3 mg/kg bw/day) or 5 to 19 (3 mg/kg bw/day only). These intervals correspond to the tabulated data presented in the report and are most likely to be correct.

[2] **This study is incorrectly referenced in EPA's Toxicology Chapter and HID Document and EPA's reference lists for each of these documents. This study was published in 1976, not 1975.**

Review of the actual study report (copy included with this submission) shows that embryotoxicity, which included increased fetal resorptions, decreased fetal weight, and delayed ossification, was evident in this study *only* at 3 mg/kg bw/day. EPA did not characterize maternal toxicity in the HID summary. As would be expected, the 3 mg/kg bw/day dose level also was maternally toxic, as demonstrated by maternal weight loss during the gestation period and marked clinical signs of toxicity.

This study predates GLP requirements and used a non-conventional dosing schedule. However, the study authors used an appropriate route of administration for developmental toxicity assessment; tested a relatively large number of dams (7 to 8 pregnant per dose group); characterized maternal toxicity; evaluated developmental endpoints including number of dead or resorbed fetuses, fetal weight, and skull-rump length; and characterized external and skeletal fetal abnormalities. The study included sufficient doses to establish a NOEL at 1.0 mg/kg bw/day for both maternal and developmental toxicity. It thus provides corroborating evidence to the Guideline rat developmental toxicity study of methyl parathion that showed no unique susceptibility to the developing fetus from maternal exposure to methyl parathion.

Kumar and Devi, 1996: This reference reports the results of a study in which methyl parathion was administered by gavage to pregnant rats at 0, 0.5, 1, and 1.5 mg/kg bw/day from GD 6 through 15. ChE levels were not tested in this study. The results of the study confirm the presence of fetotoxicity only at the 1.5 mg/kg bw/day dose level that caused marked maternal toxicity. The EPA HID discussion of maternal toxicity for this study includes only decreased weight gain (which is also the only maternal effect described in the abstract to this paper). However, review of the complete published report (copy included with this submission) shows that muscle fasciculation, tremors, lethargy, and convulsions also occurred in the dams at the 1.5 mg/kg bw/day dose level. Rather curiously, the study authors conclude the maternal toxicity at the high dose was “minimal,” which understates significantly the clinical signs in the dams.

Effects on the fetuses, including increased resorptions and decreased fetal weight, were similar to those in the previously discussed developmental toxicity study. Delayed ossification was not noted in this study. One unusual finding was noted and attributed to treatment by the study authors: an increased incidence of “hemorrhagic spots” on visceral evaluation both of the brain ventricles and cutaneous surface. The incidence was statistically significantly different from controls at the high dose when analyzed on a fetal basis; analyses on a litter basis were not done. The significance of this finding is not clear, as no similar findings have been made in any other developmental toxicity studies

of methyl parathion. It is possible that these findings were an artifact of handling and fixation. It is not reported whether the skin hemorrhages were visible on external evaluation prior to fixation. As with the other published data on methyl parathion, there is no way to evaluate the study quality because the study was not conducted in accordance with GLPs. Furthermore, there is no way to judge the accuracy of formulation, dose administration, data reporting, or analyses. Despite these questions, it is apparent that there were no treatment-related effects on development at doses that were not severely maternally toxic. Thus, the results from this study, which was adequately designed with 10 pregnant dams per dose group and included appropriate parameters for characterization of maternal and developmental toxicity, also correlate with the data from the Guideline study of methyl parathion in rats. The results do not show any unique susceptibility of the developing fetus to methyl parathion toxicity.

In Utero Exposure: Developmental Neurotoxicity

The HID Committee decision to recommend retention of the Food Quality Protection Act (FQPA) 10x factor relies heavily on the results of the study by **Gupta et al., 1985**[3] and the authors' interpretations of those results. That study evaluated a number of biochemical, morphological, and behavioral parameters in the offspring of dams dosed with methyl parathion from day 6 to 20 of gestation at 1.0 mg/kg/day ingested in a peanut butter vehicle or 1.5 mg/kg/day by gavage in peanut oil.

According to the study abstract,

> The purpose of this study was to determine the effects of subchronic administration of [methyl parathion] during gestation on behavior and development of brain cholinergic neurons in the offspring.

The authors further state:

> Little is known of the effects of OP exposure during gestation on the development of cholinergic neurons in brain. . . . In adult rats, chronic exposure to various OPs produced development of tolerance to the toxic effects [citation omitted] and a corresponding decrease in the number of muscarinic and nicotinic receptors in the brain

[3]1The study that the EPA HID document refers to was published in 1985, not 1984. An earlier study by Gupta et al., published in 1984, is cited in the 1985 article.

> [citations omitted]. The possibility that early exposure to OP may alter the developmental pattern of cholinergic receptors has not been explored.
>
> Any brief or persistent alterations in brain cholinergic neurons might be reflected in alterations in behavior, and only a few studies have investigated the behavioral or morphological effects of prenatal OP exposure.
>
> To characterize the neurobehavioral teratologic potential of MPTH [methyl parathion], we have examined the effects of subchronic prenatal exposure to MPTH on postnatal brain cholinergic neurochemistry, morphology, and behavior.

Thus, the authors were looking for physical changes in the brain tissue of pups (decreased number of receptors or other morphological changes) and confirmatory neurochemical and behavioral effects. Instead, their findings, in summary, were that methyl parathion:

1) affected acetylcholinesterase (AChE) and choline acetyltransferase activity (to a lesser extent in pups than in dams);

2) caused changes in binding to cortical muscarinic receptors in dams but not in pups;

3) caused no morphological effects in pups;

4) showed no findings different from control in pups from either dose group in the majority of the behavioral tests; and

5) showed findings different from control in four behavioral tests at the low dose level, but no findings different from control at the high dose level.

These factors support a conclusion that the study was negative for developmental neurotoxicity, that there were no effects on neurons, and that the evidence for treatment-related behavioral effects is not credible. The authors admitted in the text of the article that the "lack of a clear dose response in the several behaviors affected by MPTH is disconcerting." The use of the word "clear" is misleading—there is no dose response in the behavioral assays. They also noted that "although acetylcholine has a functional role in a number of behaviors, there is no obvious relationship between the observed neurochemical and behavioral alterations in the study." Again, the use of the word "obvious" is incorrect. In fact, the biochemical and behavioral results show a directly inverse relationship.

Despite the study's results, however, the authors chose to conclude the article by asserting that prenatal exposure to methyl parathion caused "selected subtle alterations in behavior." In the study abstract (although not in the study text), the significance of the study results was further inflated by the totally unwarranted claim that methyl parathion "altered postnatal development of cholinergic neurons."

The validity of these two conclusions that methyl parathion is critically important because, if correct, the study would provide the only existing evidence of developmental neurotoxicity. Although, as shown below, the conclusions are invalid, the HID review adopts them unquestioningly. The HID document quoted from the abstract the language about behavioral alterations and "effects on postnatal development of cholinergic neurons" three times (pages 7, 9, and 11), using it as one of the primary bases for two critical determinations: that a developmental neurotoxicity study is needed, and that the extra 10x safety factor should be retained. Moreover, the HID document does not discuss the many weaknesses in the study's design, conduct, and reporting, all of which bear on the weight the study should be given. These points are discussed in detail below.

Actual Study Observations

EPA's review does not discuss in sufficient detail what the observations actually were, in particular the observations not showing a potentially treatment-related effect. Accordingly we have cataloged the observations here.

The study showed the following with respect to effects on *dams*:

- Maternal clinical signs of ChE inhibition (e.g., several-hour periods of tremors) and decreased body weight gain during gestation were seen at the 1.5 mg/kg/day gavage dose but not at the 1.0 mg/kg/day "dietary" (peanut butter) dose.

- ChE was decreased and choline acyltransferase (CAT) was increased in the maternal brain at both dose levels.

- The binding of ^{3}H-quinuclidinyl (^{3}H-QNB) to muscarinic receptors was decreased in the frontal cortex of the maternal brain at both dose levels.

- An increase in late resorptions was seen at 1.5 mg/kg/day.

As for *pups*, the reported effect findings were:

- At 1.0 mg/kg/day, ChE was reduced in the frontal cortex of pups only on post-natal day (PND) 1, not thereafter. At 1.5 mg/kg/day, ChE reductions were seen in all pup brain regions and inhibition persisted to at least day 28.

- Increased CAT activity was seen at 1.5 mg/kg/day but was not seen at 1.0 mg/kg/day.

- Decreased latency for cage emergence and reduced accommodated motor activity were seen at 1.0 mg/kg/day but were not seen at 1.5 mg/kg/day.

- Decreased locomotor stimulation after inter-peritoneal (IP) d-amphetamine administration was observed in female pups at 1.0 mg/kg/day but not in males. No results for pups from the 1.5 mg/kg/day group were reported (see discussion below).

- Increased mean latency to bar press and days to asymptote in rate of bar pressing in operant conditioning tests were noted at 1.0 mg/kg/day but were not seen at 1.5 mg/kg/day.

The following parameters were reported as not affected in pups:

- There were no effects on litter size or on pup body and brain weights.

- There were no effects on the post-natal pattern of body weight and brain weight gain (data not presented).

- The binding of ^{3}H-QNB was not affected in the pups at either dose.

- No effect was seen on pre-weaning reflexive behavior, startle response, passive avoidance, shuttle box avoidance, or rotorod performance at either dose in either sex.

- No gross structural abnormalities were evident.

- Histopathological evaluation of brains from control and 1.5 mg/kg/day 28-day pups showed no differences in density of pyramidal cells in the hippocampus, granular cells in the cerebellum, presence of heterotropic cell groups, or other abnormalities.

<u>The Observations Do Not Support the Critical Conclusions</u>

The foregoing discussion shows that the neuropathological or morphological examinations in pups did not-show treatment-related effects; no physical evidence

of alterations in neural development were seen. The only biochemical effect of interest was that multiple daily doses of dams until just before pups are born produces expected reduction in pup cholinesterase levels at birth and for a period of time thereafter, which is not a developmental effect. Any argument that the study furnishes evidence of altered neuronal development thus must rest entirely on observations of behavioral effects. But there are three substantive reasons to conclude that the results of the behavioral assays do *not* show a treatment-related effect from exposure to methyl parathion:

> First, no dose response was evident for the behavioral study findings (in contrast, a clear dose response was evident for clinical signs of toxicity in the dams and for changes in biochemical endpoints in the dams and, to a lesser extent, in pups). Although, as noted below, a direct assessment of dose response cannot be made due to the differing routes of administration in this study, it would be anticipated that treatment-related effects would be more pronounced in the high-dose group, both because of the greater exposure level and because of the bolus route of administration. Neither the cage emergence, accommodated locomotor activity, nor the operant conditioning results showed any evidence of dose response. As for the fourth test with "positive" low-dose results, the d-amphetamine locomotor stimulation assay, no results were reported for the high dose animals; either the test was conducted only for the low-dose level rats, or the high-dose results were not reported.
>
> Second, the behavioral findings do not correlate to the biochemical findings; in fact, there is an *inverse* relationship between the severity and nature of biochemical findings and the presence of the behavioral "effects."
>
> Third, there are inconsistencies even within the "positive" behavioral assays. In the locomotor stimulation after d-amphetamine administration assay, the group that was exposed to methyl parathion but not to amphetamine showed no changes in activity compared to control, in contrast to the locomotor activity changes reported for the low-dose-group animals in the accommodated locomotor activity assay. The study authors themselves question the results of the locomotor stimulation after d-amphetamine administration assay.[4]

While the authors speculate that there may be some reason why there was no behavioral effect at high doses and an inverse relationship with the cholinesterase

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[4] The authors state that the decreased response in females compared to males could be due to an artifact caused by the "usually greater response of females to d-amphetamine." They also speculate, as an unsupported hypothesis, that exposure to methyl parathion "may have influenced the estrogen balance in the females and thus modified their behavior selectively." Cheminova is aware of no evidence of endocrine disruption associated with exposure to methyl parathion (this agrees with the EPA assessment summarized on page 10 of the HID document).

effects, they offer no pertinent data and ultimately conclude only that the matter requires "further study." They do not discuss the possibility that the differences from control seen in the low dose group in some of the behavioral tests may simply reflect normal variability in a population. No attempt was made by the authors to analyze data on a functional domain basis, or to evaluate the lack of correlation of results between different behavioral tests. There is no indication that the authors attempted to replicate their findings; or that this has been done by other investigators.

In conclusion, in this study methyl parathion predictably caused alteration of enzyme activities in certain brain regions in both adults and pups, but there was no evidence of unique susceptibility of the young to these changes, and no evidence that the pups were more susceptible than the adults.[5] As discussed in detail above, findings in the behavioral assays do not show any treatment-related adverse effects, in view of the absence of dose response and the absence of correlation to biochemical effects. Further, the authors found no evidence of any morphological or microscopic neural developmental abnormality in pups of dams exposed to overtly toxic doses of methyl parathion. The study results do not show credible evidence of developmental neurotoxicity. The study provides no evidence at all of altered post-natal development of cholinergic neurons, even though that "finding" was set forth in the abstract and cited repeatedly in the EPA HID document.

The Study Suffers from Numerous Design and Conduct Limitations and Problems

EPA's review of the Gupta et al. study results also does not include a discussion of the study's limitations, which directly affect interpretation of the treatment-relationship of the study findings and, for this reason, are relevant to the weight that the study should be given in a "weight of the evidence" assessment. The following discussion raises several major problems that would disqualify the study from serious consideration if submitted by a registrant in support of the product. Problems like these are frequent in published studies. In most cases it is impossible to resolve questions because (a) the study data are incomplete or unarchived, or (b) the study authors simply refuse access to whatever raw data may exist.

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[5] EPA itself concluded in the HID document (pages 10- 11) that

> **No indication of additional sensitivity of the offspring was suggested by the [Gupta et al.] data, since offspring effects were noted concurrently with maternal effects.**

This HID conclusion regarding the absence of unique or additional susceptibility of the offspring in this study is obviously correct. However, four paragraphs later (page 11), the Gupta et al. study is cited as providing "qualitative evidence" of "increased sensitivity to the offspring." These two statements are in direct conflict, and the second statement is unsupported.

The Gupta et al. study has the following general weaknesses:

- Very small group sizes were evaluated.
- There was no analytical characterization of dose.
- Reporting of methods and data was selective and incomplete.
- The study obviously was not conducted in accordance with GLP.

Additional deficiencies in study design and reporting limit the conclusions that can be drawn from the biochemical assays in this study.

- Definitive conclusions regarding the presence or absence of dose response cannot be drawn because of to the difference in routes of administration between the two dose levels.
- Each dose group had a control group dosed by the appropriate route. However, for the data tables for maternal cortical ChE, CAT, or ^{3}H-QNB binding, or for pup ^{3}H-QNB binding, it cannot be determined *which* control group findings were used for comparison to the treated groups because results from only a single control group are shown (see Table B-3 in the publication for an example).
- Pup ChE data are presented as a percent of control, but it is not clear whether the control values were derived from the appropriate oil gavage and peanut butter ingestion control groups.
- Table B-1 in the published study appears to be inaccurate, because it represents, according to the title, *maternal* ChE activities and ^{3}H-QNB binding, while a footnote states that the data represent the mean of six or seven *litters*.

There are also significant problems with the design, interpretation, and reporting of the behavioral assays in this publication, as outlined below.

<u>i. Cage Emergence and Accommodated Locomotor Activity Tests</u>

Weaknesses in design of these tests include:

- Parameters were tested only at a single interval (at 3 months of age for cage emergence and at 2 months of age for accommodated

locomotor activity). Repeated testing with replicated findings would provide more confidence in the data.

- Cage emergence, as evident from the high standard deviations, is a variable measure that is susceptible to confounding due to noise, light, smell, cage positioning, and reaction of the observer.

- There is no indication that litters were culled or standardized for either sex or group size. The number of pups tested varied among groups, and no analyses by litter were conducted.

- Parameters were not reported by pup sex (the text does not state whether evaluations were conducted separately by sex). The sex ratios in the tested population of pups were not defined. Because female rats tend to show more aggressive exploratory behavior than do males, variances in sex ratios between controls and treated groups of pups could alter the response for both cage emergence and locomotor activity parameters.

ii. D-Amphetamine Stimulated Locomotor Activity Test

It is difficult to evaluate either the treatment relationship or the biological significance of the results of this test for the following reasons:

- The text does not specify how old the pups were for the d-amphetamine stimulated locomotor activity test.

- The text does not state whether pups in the 1.5 mg/kg bw/day group were tested (the absence of these data is suspect because all other behavioral parameters were tested at both dose levels).

- The publication cites no reference for methodology for this test, which is not a standard neurobehavioral assay.

iii. Operant Conditioning Test

The operant conditioning test results are also difficult to interpret for the following reasons:

- The test was done on "3 to 6 month old rats," which is a wide age range, and the text does not specify if the age distribution was randomized between the treated and control groups.

- It is not clear if four litters were tested per dose group or if four pups were tested per dose group.

- The results are not analyzed separately by pup sex.

In summary, if this study is used in a weight-of-the-evidence evaluation of potential neurotoxicity, the deficiencies in the study should be fully described. Based on a detailed evaluation of the study limitations, Cheminova lacks confidence in the reported results and believes EPA should not rely on it as a predicate for regulation.

Direct Administration to Pups

The HID document includes summaries of the published studies in which methyl parathion is injected directly into pups at high dose levels. In general Cheminova concurs with EPA's summaries of the journal articles. These studies do not; however, provide a basis for any additional safety factor based on pup susceptibility or for requiring a developmental neurotoxicity study because of the inappropriate routes of administration and high dose levels used in these studies.

The EPA HID document reviews the following studies in which methyl parathion was administered directly to pups.

Benke and Murphy, 1975[6]: This study shows only that at a severely toxic or lethal dose range, lethality occurs in directly dosed younger pups at a lower dose level than it occurs in adults. There is no evidence from this study, however, that the susceptibility of the pups exceeds the 10-fold standard factor for intra-species extrapolation. In fact, there was a less than 10-fold difference in susceptibility between younger pups and adults. The interperitoneal injection technique used in the study is stressful to the animals and has a high potential for creating serious or fatal injection trauma, particularly when dosing is to newborn pups. No vehicle control group was tested in this study, so possible mortality due to injection technique could not be assessed. This problem could have contributed to the markedly increased mortality in the day one pups. Because of this problem, the study is not useful for drawing conclusions regarding differential susceptibility of very young pups.

[6] This study is incorrectly identified in EPA's Toxicology Chapter and HID Document and EPA's reference lists. This study was published in 1975, not 1974.

Pope et al., 1991 assessed the time course of cholinesterase (ChE) inhibition and recovery in whole brain, comparing the findings after nonlethal acute maximum tolerated doses (MTDs) of methyl parathion to neonatal (7-day-old) and adult rats. Methyl parathion was dissolved in peanut oil and administered subcutaneously (sc). A less than two-fold difference in the MTDs was determined for the 7-day-old pups compared with the adult pups (7.8 mg/kg versus 18 mg/kg, respectively). Body weight gain was more inhibited in adults than in the pups. Brain ChE inhibition was comparable on the day of treatment for both groups; recovery, however, was more rapid in neonates. In a second sc study**, Pope and Chakraborti, 1992** compared brain ChE ED_{50} values in adult and neonatal rats four hours after sc exposure to methyl parathion. An approximate nine-fold difference in inhibitory potency was noted for methyl parathion. However, it is not possible from this study to quantitatively assess pup susceptibility because of potential differences of absorption from the sc injection site in pups and adults. Additionally, the route of administration is not relevant to potential human exposure situations.

4. Chlorpyrifos data

In the HID review, EPA mentions that in a chlorpyrifos study (no citation provided), a more than 10-fold difference in susceptibility was seen between adults and young. It is not clear from the HID document why EPA has concluded that the chlorpyrifos data are relevant to the assessment of pup susceptibility to methyl parathion. Chlorpyrifos is not structurally similar to methyl parathion and shows a different pattern of toxicity.

5. Reasons for sensitivity of young test animals to high-dose cholinesterase inhibitors

The enhanced toxicity to neonatal and young rodents of methyl parathion at high dose levels is not due to differences in target sensitivity for toxicity because brain ChE from neonates and adult rats is equally sensitive to inhibition. Activation to the more toxic oxon form of methyl parathion is also decreased in neonatal rats. The lethal dose and the MTDs are lower in neonatal rats dosed directly than in adults because neonatal rats have lower levels of hepatic aliesterase and p-450 mediated dearylation. At birth, levels of these enzymes are low, but they increase rapidly during the period the rat is nursing (Atterberry et al., 1997).

No data were found on the developmental time-course of these enzymes, per se, in human infants, although humans have considerably advanced development at birth compared with rats. Augustinsson and Barr (1963) and Augustinsson and Brody (1962) found that in human infants the activity of

serum arylesterase exceeds 50% of adult level by 2 months of age and reaches adult levels by 6 months of age.

Because the primary influence on the differential susceptibility of pups and adults to methyl parathion is the level or activity of detoxifying enzymes, one cannot accurately extrapolate or predict differential susceptibility from high dose exposures, in which the available detoxifying enzymes are saturated, to low levels more representative of potential human exposures. In the report of the March 24-25, 1998, Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Committee, the Panel suggested that

> the magnitude and difference of the sensitivity between adults and juveniles should be determined more thoroughly . . . much of this information was generated in acute treatment experiments, frequently at very high exposure levels. Such data may not be appropriate to extrapolate to low-dose situations, e.g., organophosphates, where much, if not all, of the age-related differences may be attributable to differences in the magnitude and activity of detoxification enzymes. *In such cases, differences in toxicity between adults and juveniles would be substantially greater at high doses where detoxification mechanisms are saturated than at low dose levels where they are not* (emphasis added).

D. ABSENCE OF DEVELOPMENTAL NEUROTOXICITY STUDY

No developmental neurotoxicity study has been conducted for methyl parathion, nor had EPA ever indicated that a developmental neurotoxicity study of methyl parathion was needed until the HID document was issued. No data call-in for this study has been issued to date.

Cheminova believes that the existing data on methyl parathion do not support a data requirement for this study, for several reasons:

- There is no evidence of adverse effects on brain or nervous system development in the Guideline developmental toxicity studies of methyl parathion.

- Pup growth and development is not affected at low-dose exposures to methyl parathion, based on Guideline reproductive toxicity study data.

- Low-dose neurotoxic effects (brain ChE inhibition and clinical signs) are transient and reversible.

- Neuropathological effects from short-term exposures are present only after administration of severely toxic or lethal doses of methyl parathion.

- As discussed in detail in the preceding section, the published studies claiming effects of methyl parathion on neural development do not provide reliable evidence of any specific developmental neurotoxic effect.

The absence of a developmental neurotoxicity study should not be used as a reason for requiring an additional safety factor unless there is substantial evidence from the existing data of concern about developmental neurotoxicity. See the discussion of this issue in the Implementation Working Group's issue paper entitled "The FQPA Additional Uncertainty Factor". The existing data for methyl parathion give no reason to expect that fetuses, infants, or children may have any special susceptibility to methyl parathion from exposure at any reasonably foreseeable dose levels. The basis for requirement of a developmental neurotoxicity study that EPA has recently proposed is derived primarily from EPA's noncritical adoption of the misleading claims of the authors in Gupta et al., 1985. A secondary basis for the the requirement appears to be the assumption in EPA's still-developing test triggers that any neuropathological effects are a proper basis for requiring the study, without analyzing whether the observed effects have any predictive value for developmental neurotoxicity. The reliable data do not predict that a developmental neurotoxicity study would show adverse developmental effects. Cheminova does not believe conducting a developmental neurotoxicity study would provide new information on potential adverse effects of exposure to methyl parathion. Even if EPA ultimately requires the study be performed (which it has not yet done), EPA should not apply the 10X extra safety factor at this time.

III. REVIEW OF NEUROTOXICITY STUDIES

A. ACUTE NEUROTOXICITY

The results of the methyl parathion acute neurotoxicity study are used by EPA to (1) support the additional 10-fold safety factor for infants and children, based on what EPA concludes is a low no-observed effect level (NOEL) for neuropathological findings, and (2) derive the NOEL used as the basis for the acute and short-term dietary risk calculations. EPA's decisions on both these points are overly conservative for several reasons discussed below.

The acute neurotoxicity study, as required by EPA guidelines, is a bolus gavage study, which is questionably relevant to a dietary exposure scenario. This study guideline was developed to be a screen for neurotoxicity (not to provide a NOEL for any endpoint for risk calculations), and very high and toxic doses were

intentionally administered in accordance with the guideline, far exceeding any conceivable dietary intake. It should be noted that the mid and high dose levels in the methyl parathion acute neurotoxicity study exceed the value cited by EPA as the lethal dose 50% (LD_{50}) for an oral acute dose of methyl parathion.

Based on EPA recommendations, the low dose was selected to provide a NOEL for any evidence of cholinesterase (ChE) inhibition. Because ChE data were required to be obtained at the "time of peak effect," and no existing data were available for this time point to assist in setting the appropriate dose levels for the study, a very low dose level was selected as the low dose. No effects were seen at the low-dose level in this study, so this dose level was defined as the NOEL. It is clear, however, from other study data, as well as from the pattern of effects seen at the mid- and high-dose in this study, that the actual NOEL for findings other than transient ChE inhibition is likely to be significantly higher than the low dose level that was tested.

Based on the subchronic neurotoxicity study results discussed subsequently, the no-observed adverse effect level (NOAEL) for an acute **dietary** intake (as opposed to a gavage intake) is likely to be substantially higher.

Hence, the concern regarding the low acute NOEL for neurotoxicity is misplaced. As noted earlier, Cheminova is developing additional data to more accurately characterize the NOEL from an acute oral (dietary) exposure to methyl parathion.

A summary of the acute neurotoxicity study design and results is presented below.

Minnema, 1994a (MRID 43254401): Sprague-Dawley rats were given single bolus doses by gavage of methyl parathion in a corn oil vehicle at dose levels of 0, 0.025, or 7.5 mg/kg (males and females), or 10.0 mg/kg (males only), or 15.0 mg/kg (females only). For each dose group, 10 males/sex per group were designated for neurobehavioral assessment (6 of these animals were subsequently perfused for neurohistopathological evaluation); 5 animals/sex/group for plasma, RBC, and regional brain ChE evaluations at time of peak effect (1.5 hr post-dose); and 5 animals/sex/group for ChE evaluations at 2 weeks post-dose (control and high-dose groups only).

Animals received functional observation battery (FOB) and motor activity assessments at time of peak effect and at days 7 and 14 after dosing, were observed for clinical signs daily, and were weighed weekly. Gross necropsies were done on unscheduled deaths and scheduled sacrifices. Microscopic evaluations were performed on the following perfused nervous system tissues: brain with brainstem; eyes with optic nerve; cervical and lumbar dorsal and ventral root fibers; cervical, lumbar, and mid-thoracic spinal cord; cervical and lumbar dorsal root ganglia;

Gasserian ganglia; and sciatic, sural, and tibial nerves. In addition, the pituitary, selected muscles, and any macroscopic lesions were examined.

Mortality (3/10) occurred in the high-dose male (10 mg/kg) and female (15 mg/kg) groups, showing these doses were very close to an acute LD_{50}. In the mid- and high-dose males and females, clinical signs typical of ChE inhibition were seen at the time of peak effect; many of the FOB parameters were affected, and RBC, plasma, and regional brain ChE were predictably inhibited. No clinical signs of toxicity were evident at days 7 and 14. Both plasma and RBC ChE were still partially inhibited 14 days after dosing but was showing a strong trend toward recovery.

Neuropathological evaluation showed an increased incidence of myelin lesions in the high-dose males and females, and a marginal, possibly treatment-related effect in the males at 7.5 mg/kg. No treatment-related findings were seen in males at 0.025 mg/kg. Females at 0.025 mg/kg were not evaluated due to the absence of treatment-related findings in females at 7.5 mg/kg. Findings are summarized in Table B-11.

Table B-11. Incidence of Demyelination in Acute Neurotoxicity Study in Rats With Methyl Parathion

	Male				Female		
Dose (mg/kg)	**0**	**0.025**	**7.5**	**10.0**	**0**	**7.5**	**15.0**
Number Examined	6	6	6	6	6	6	6
Number Affected	3	4	5	6	4	0	6
Site							
Cervical Spinal Cord	—	NA	NA	—	—	NA	—
Dorsal Root Fiber	—	NA	—	3	—	—	—
Ventral Root Fiber	—	NA	—	2	1	—	—
Lumbar Spinal Cord	—	NA	—	1	—	—	—
Spinal Nerve	—	NA	—	1	1	—	—
Dorsal Root Fiber	—	3	4	5	2	—	5
Ventral Root Fiber	2	3	4	4	1	—	3
Sciatic Nerve	1	NA	—	3	1	—	1
Tibial Nerve	—	—	1	3	1	—	1
Sural Nerve	—	NA	—	2	—	—	—

NA = Not Applicable
— = Unremarkable

The high-dose rats show an increased incidence of demyelination, compared with the incidence in the control animals. The lesion was characterized microscopically by small and localized foci of myelin vacuolation and fragmentation. The lesion was also observed in control animals. The lesion was the same histomorphologically in the control and dosed groups. There was a minor increase in severity of this finding (from minimal to slight) in the high-dose group compared with the controls. Mid-dose (7.5 mg/kg) females did not show an increased incidence for this finding; in contrast, no mid-dose females were affected. The response seen in the mid-dose males is considered marginally treatment-related based on several factors:

- relatively few nerve fibers were affected;

- there was no increase in severity of the lesion in the mid-dose group compared with controls (the lesions were considered minimal in severity in both groups); and

- the distribution of the lesions was even less than that observed in the female control group.

The study director concluded that "the significance of this lesion is unclear, as the severity was mild (sic), no functional correlates with the lesion were noted, and the increased incidence of the lesion was associated with extremely stressful (near lethal or lethal) levels of Methyl parathion technical exposure…."

There are several misstatements in the HID document regarding the neuropathological findings at 7.5 mg/kg. On pages 9 and 10, a summary of findings at the 7.5 mg/kg dose level states there was "focal demyelination of the dorsal and ventral root fibers of the *cervical* and lumbar spinal cord and focal demyelination of the *sural* and tibial nerves." However, review of the histopathological incidence data shows an increased incidence of focal demyelination at 7.5 mg/kg compared with control in male animals only, and only in the dorsal and ventral root fibers of the lumbar spinal cord (and none in the cervical spinal cord). A single incidence of focal demyelination of the tibial nerve was seen at this dose level, and no lesions of the sural nerve were evident at 7.5 mg/kg.

Further, the review of this study in the HID document on pages 17 and 18 fails to mention the presence of an increased incidence of focal demyelination in the high-dose (15 mg/kg) females, the absence of findings in females at 7.5 mg/kg, or the marginal nature of the findings in males at 7.5 mg/kg. Careful assessment of the potential biological significance of the findings in the mid-dose males is critical because the presence of lesions in this group is used as one of the bases for adding a 10-fold safety factor.

It is correctly stated in the HID review that clinical signs at the 7.5 mg/kg dose level were transient and reversible, and the conclusions regarding ChE inhibition are correct, although a clear trend toward recovery from ChE inhibition was noted at 14 days. The statement in the HID document (page 12) that neuropathology was evident at the "relatively low dose of 2.5 mg/kg" is not correct. Rather, as discussed above, treatment-related slight myelin degeneration was seen in males at 10 mg/kg, and in females at 15 mg/kg. Both dose levels showed lethality (3/10) for the respective sexes. Equivocally treatment-related neuropathological findings were seen in the 7.5 mg/kg dose group (in males only), which was also a severely toxic dose. The marginal nature of this finding in males and the absence of any such findings in females suggests that 7.5 mg/kg either is or is very close to a NOEL for neuropathology. No dose of 2.5 mg/kg was tested in the acute neurotoxicity study of methyl parathion; this appears to be a typographical error in the HID document.

SUBCHRONIC NEUROTOXICITY STUDY

The HID review document does not provide a full review of the oral subchronic neurotoxicity study with methyl parathion. Review of these data, however, may assist in (1) interpreting the significance of the histopathological nervous system lesions in the acute neurotoxicity study; and (2) estimating an acute dietary NOEL.

Minnema, 1994 (MRID 43490501): In the subchronic neurotoxicity study with methyl parathion, Sprague-Dawley rats were dosed with diet containing 0, 0.5, 5, or 50 ppm of methyl parathion for 3 months. Based on actual compound consumption data, the mean dose levels in this study were 0, 0.03, 0.31, and 3.12 mg/kg bw/day in males, and 0, 0.04, 0.37, and 4.05 mg/kg bw/day in females. (Figures B-1 through B-6, and Tables B-19 through B-21 in the appendix to this attachment [Appendix B] provide Cheminova's estimates of the test material consumption values for this study. These values vary slightly from those calculated by EPA.)

Animals received FOB and motor activity assessments pretest and during study weeks 4, 8, and 13; were observed for clinical signs daily; and were weighed weekly. In addition, food consumption was recorded weekly. Satellite animals were evaluated for plasma and RBC ChE activities at the same intervals as the FOB and Motor Activity assessments; brain ChE was tested at termination. Gross necropsies were done on unscheduled deaths and scheduled sacrifices. Microscopic evaluations were performed on the following perfused nervous system tissues for 6 animals/sex/dose group): brain with brainstem; eyes with optic nerve; cervical and lumbar dorsal and ventral root fibers; cervical, lumbar, and mid-thoracic spinal cord; cervical and lumbar dorsal root ganglia; Gasserian ganglia; and sciatic, sural, and tibial nerves. In addition, the pituitary, selected muscles, and any macroscopic lesions were examined.

There was no treatment-related mortality. Decreased body weight and food consumption were seen in males and females at 50 ppm. Neurobehavioral signs were seen primarily in females at 50 ppm, including decreased hindlimb grip strength, increased latency to first step in the open field, tremors, and absent pupillary responses. There were no neurobehavioral effects at the 5 and 0.5 ppm dose levels. Brain, plasma, and RBC cholinesterase inhibition was evident at 50 ppm; substantial recovery was seen in animals switched to untreated diet for 3 weeks after the 13-week dosing period. RBC cholinesterase was also inhibited at 5 ppm (25 to 27% decrease compared with control). Because the degree of RBC inhibition at 5 ppm was relatively slight (close to 20%) and there was no evidence of brain cholinesterase inhibition, clinical signs of toxicity, or neurobehavioral effects in a rigorous series of neurotoxicological evaluations, Cheminova believes the NOAEL for cholinesterase inhibition in this study is very close to 5 ppm. The NOEL for neurobehavioral effects and for inhibition of brain cholinesterase was 5 ppm.

Page 10 of the EPA HID document states that in the subchronic neurotoxicity study "the incidences of degenerative lesions of peripheral nerves at 50 ppm . . . were equivocal." Table B-12 shows the incidence in the subchronic neurotoxicity study of peripheral nerve histopathological findings.

Table B-12. Incidence of Minimal Axonal Degeneration Observed in the Subchronic Neurotoxicity Study With Methyl Parathion

	Male				Female			
Dose (ppm)	**0**	**0.5**	**5**	**50**	**0**	**0.5**	**5**	**50**
Number Examined	6	0	0	6	6	0	0	6
Site								
Cervical Spinal Cord	—	NA	NA	—	—	NA	NA	—
Dorsal Root Fiber	—	NA	NA	—	—	NA	NA	—
Ventral Root Fiber	—	NA	NA	—	—	NA	NA	—
Lumbar Spinal Cord	—	NA	NA	—	—	NA	NA	—
Dorsal Root Fiber	—	NA	NA	1	1	NA	NA	1
Ventral Root Fiber	—	NA	NA	2	1	NA	NA	1
Sciatic Nerve	1	NA	NA	1	1	NA	NA	1
Tibial Nerve	2	NA	NA	—	—	NA	NA	—
Sural Nerve	—	NA	NA	—	—	NA	NA	1

NA = Not Applicable
— = Unremarkable

These minimal lesions, which are characterized by localized segmental swelling of individual axon fibers, and the formation of degenerating myelin "ovoids" within the swollen segments, occur spontaneously in untreated animals. The study pathologist concluded that "these subtle lesions were typical of those occasionally seen in normal populations of rats of this strain and age and were distributed among the examined dose groups with no suggestion of any effect of methyl parathion exposure."

There is no evidence of a treatment-related increase in peripheral nerve fiber degeneration in the high-dose animals compared with controls, based on either increased incidence or increased severity of lesions (all were minimal) or an increased distribution of the lesions.

It is not clear why EPA now considers the treatment-relationship of peripheral nerve lesions at 50 ppm to be "equivocal." The Data Evaluation Record (DER) for the subchronic neurotoxicity study (Fricke, 1996) in fact concluded that there was no treatment-related neuropathology in this study. The DER stated "degenerative lesions were observed in the peripheral nerves of high-dose males and females. . . . These lesions were not suggestive of a treatment-related effect since the incidences of the lesions was low and also observed in control animals." Cheminova concurs that there is no evidence of treatment-related neuropathology in this study. Further,

if EPA had decided there were treatment-related effects at the high dose, it would have requested evaluation of the mid and/or low-dose level animals from this study to clarify the treatment-relationship and to establish an NOEL. No such evaluation, however, was requested by EPA. Cheminova believes that the NOEL for treatment-related neuropathological lesions in this study is 50 ppm (HDT).

RAT CHRONIC (TWO-YEAR) STUDY

Daly et al. 1983 (Accession Nos. 00252501, 00252501, 00252503, 00253346, 00253372, 00253373, 00253374): In the chronic rat study, methyl parathion was administered at 0, 0.5, 5, or 50 ppm in the diet (equivalent to approximately 0, 0.02, 0.21, and 2.21 mg/kg bw/day for males, and 0, 0.03, 0.29, 3.34 mg/kg bw/day for females) to Sprague-Dawley rats for 26 (males) or 28 (females) months. Body weights and food consumption were recorded weekly to week 14 and biweekly thereafter. Clinical pathology parameters were measured pretest and at 6, 12, 18, and 24 months. Ophthalmic evaluations were done pretest and at 3, 12, and 24 months for both sexes, and at 28 months for females only. Brain cholinesterase was measured at termination; all animals were examined grossly at necropsy and microscopic evaluations were done. Neuropathological evaluations (5/sex/dose) of nervous system tissue including brain, spinal cord, and sciatic nerve were done. It should be noted that there was a high rate (approximately 50%) of intercurrent infection (interstitial pneumonia) in animals in this study. Results of this study are outlined below.

At the 50 ppm (2.21 or 3.34 mg/kg bw/day, males and females, respectively) dose level, treatment-related clinical signs included tremors, alopecia, and abnormal gait, primarily in females. Decreased mean body weights were noted in both males and females; decreased food consumption was noted in females. Decreases in hematocrit (Hct), hemoglobin (Hgb), and RBC were noted in females at 6, 12, 18, and 24 months, and in males at 24 months. Decreased plasma ChE in males and females occurred from month 6 to termination. Decreased RBC ChE in males occurred from month 6 to termination, and in females at months 12 and 18. Decreased brain ChE at termination was seen in both males and females. Retinal degeneration (at 24 months and at termination) and an increased number of cataracts (at termination) were seen in females. Sciatic nerve degeneration was seen in high-dose males, and was somewhat more severe than that seen in control animals.

At the 5 ppm (0.21 or 0.29 mg/kg bw/day, males and females, respectively) dose level, one female was noted with abnormal gait (seen later in the study [78 weeks] than the observed instances in the high-dose group [48 weeks] and considered unlikely to be related to treatment). Marginally decreased Hct, Hgb, and RBC was noted in males at 24 months within the normal range in an older rat population. Slight, nonstatistically significant decreases (<11% compared with controls) in

erythrocyte cholinesterase was noted in both males and females. None of these findings at 5 ppm represents convincing evidence of an adverse treatment-related effect.

At the 0.5 ppm dose level, no treatment-related effects were seen.

Significant controversy exists regarding a NOEL for peripheral nerve effects in this study. Interpretation of these data is made difficult by the small number of animals and tissues examined—2 sites on the sciatic nerve for 5 animals/sex/dose group, and the relatively high background incidence of degenerative changes to the sciatic nerve, typical of older rats, particularly males, maintained in wire-bottomed cages (Eisenbrandt, et al., 1990).

The study authors concluded that histopathological findings in the 5 pm dose group "could not be distinguished from those of the controls." The HID document states that the original EPA review of these data concluded there was no NOEL for peripheral nerve effects, but that a subsequent EPA review indicated the NOEL was 0.5 ppm. Cheminova does not have copies of either EPA review for this study.

Sciatic nerve findings in the two-year chronic rat study are presented in Table B-13.

Females showed no lesions of the proximal sciatic nerve and no suggestion of a dose response for the distal sciatic nerve lesions. The NOEL for female rats for neuropathological findings in peripheral nerves following chronic dietary exposure to methyl parathion should be established as 50 ppm (HDT). Males generally show an increase in the severity and incidence of lesions at 50 ppm, but, as mentioned, the small numbers evaluated and the high background incidence of lesions makes ascription to methyl parathion exposure equivocal. Males in the mid-dose group showed no clearly treatment-related increase in incidence or severity of either distal or proximal sciatic nerve lesions. Cheminova believes the NOEL for males for equivocally treatment-related peripheral nerve lesions in this study should be at least 5 ppm. The overall NOAEL from this study for adverse treatment-related effects should also be 5 ppm (0.21 or 0.29 mg/kg bw/day for males and females, respectively).

Table B-13. Incidence and Severity of Brain, Spinal Cord, and Sciatic Nerve Lesions in the Two-Year Chronic Methyl Parathion Study in Rats

(Note: Severity range was calculated by a Cheminova reviewer.)

Tissue	Male				Female			
Dose (ppm)	0	0.5	5.0	50	0	0.5	5.0	50
Brain (No. Eval.)	5	5	5	5	5	5	5	5
Within Normal Limits	5	5	5	5	5	5	5	5
Spinal Cord (No. Eval.)	5	5	5	5	5	5	5	5
Within Normal Limits	5	5	5	5	5	5	5	5
Sciatic Nerve—Proximal (No. Eval.)	5	5	5	5	5	5	5	5
Myelin Sheath Degeneration	2 (2)	5 (1-3)	4 (1-2)	5 (1-4)	0	0	0	0
Ballooning	3 (1-2)	5 (2-3)	4 (1-3)	5 (2-3)	0	0	0	0
Schwann Cell Proliferation	4 (1-3)	5 (1-3)	4 (1-3)	5 (2-3)	0	0	0	0
Perivascular Myelin Debris	5 (1-3)	2 (1-2)	2 (1)	3 (1-2)	0	0	0	0
Loss of Myelinated Fibers	2 (1-2)	2 (1-2)	4 (1-2)	5 (2-3)	0	0	0	0
Cholesterol Clefts	0	0	0	1 (3)	0	0	0	0
Sciatic Nerve—Distal (No. Eval.)	5	5	5	5	5	5	5	5
Myelin Ovoids	2 (1)	0	2 (1-2)	5 (1-3)	0	0	0	0
Sciatic Nerve—Distal (ctd.)								
Myelin Sheath Ballooning	5 (1-3)	5 (2-3)	3 (1-4)	5 (2-4)	1 (2)	1 (2)	3 (1-2)	2 (1-2)
Loss of Myelinated Fibers	5 (1-3)	5 (1-3)	5 (1-3)	5 (1-4)	0	2 (1-2)	1 (1)	2 (1)
Segmental Demyelination	5 (1-2)	5 (1-2)	5 (1-3)	5 (1-4)	1 (2)	3 (1-2)	4 (1-2)	1 (1)
Remyelinated Fibers	5 (1-2)	5 (1-2)	5 (1-3)	5 (2-4)	0	3 (1-2)	1 (1)	2 (1)
Schwann Cell Proliferation	5 (1-2)	5 (1-2)	4 (1-3)	5 (2-4)	1 (1)	1 (1)	3 (1)	0
Myelin Phagocytosis	4 (1-2)	5 (1-2)	4 (1-3)	5 (2-4)	0	1 (2)	2 (1)	1 (1)
Cholesterol Clefts	0	0	1 (4)	2 (1-4)	0	0	0	0

KEY: 1 - minimal 2 - mild 3 - moderate 4 - marked 5 - severe

RAT CHRONIC 12-MONTH STUDY

Daly, 1991 (MRID 41853801): The HID review fails to mention this 12-month chronic toxicity study of methyl parathion in rats that was done specifically to evaluate and develop a NOEL for potential effects on eyes and nervous system tissue in an effort to upgrade and supplement the two-year chronic rat study. The HID review also does not include a discussion of the supplements to the special eye and nerve study (consisting of an evaluation of electroretinogram (ERG) data submitted to EPA on January 4, 1994 and the recent reevaluation of sciatic and tibial nerve tissues from the 12-month methyl parathion rat study submitted to EPA on January 23, 1997).

In the EPA review of this study (REF 6/14/93; received by Cheminova on 7/29/93), EPA suggested a peer review of the sciatic nerve slides from the lower dose levels be performed to determine a NOEL for neurotoxic effects. EPA also requested additional data for this study, including retinal pathology, description of ERG analyses, and additional statistics on the ERG data.

Supplementary ocular data were submitted to EPA in May of 1991 (MRID 41853801 Supplement). Cheminova received a response in April 1996, indicating that the ocular data were acceptable and no treatment-related ocular effects were present. This response also indicated that due to a lack of consensus for a NOEL for neuropathology, Office of Pesticide Programs was not making a decision to upgrade the original chronic study at that time. EPA stated that it would reevaluate all existing data <u>including a sub-chronic neurotoxicity rat study</u> (discussed above) to ascertain if a NOEL for neurotoxicity could be achieved. (There is no indication that a comprehensive reevaluation was done by EPA.)

At the Agency's request, Cheminova undertook a peer review of peripheral nervous tissue slides from the one-year study to assist EPA in making a decision regarding a NOEL for neurotoxicity **Brennecke, 1996 (MRID 44204501).** Certain limitations in the available data precluded a full "peer review" evaluation, including the unavailability of the original pathologist due to illness; lack of identification by the original pathologist of which nerve sections were evaluated for each animal (each slide contained multiple sections); poor quality of some of the slides and/or sections; and labeling problems for some of the slides. These limitations were discussed in detail in conversations in June of 1996 between Drs. Judith Hauswirth (Jellinek, Schwartz & Connolly, Inc.) and Clark Swentzal (EPA Toxicology Branch II, HED), and the procedures to be used in the neuropathological reevaluation were agreed to by EPA prior to the reevaluation.

A summary of Daly, 1991study and the results of the Brennecke, 1996 reevaluation follow.

In the 12-month chronic study, methyl parathion was administered in the diet to Sprague-Dawley rats at doses of 0, 0.5, 2.5, 12.5, or 50 ppm. Compound intakes were 0, 0.020, 0.107, 0.533, and 2.207 mg/kg bw/day for males, and 0, 0.026, 0.138, 0.697, and 3.088 mg/kg bw/day for females. Animals were divided into two subgroups: subgroup A, with 50 rats/sex/group, used for neurotoxicity and ChE evaluations, and subgroup B, with 20 rats/sex/group used for ocular evaluations. All animals were observed for clinical signs, and body weight and food consumption were monitored. Plasma and RBC ChE evaluations were done on 10/sex/dose at months 1, 3, 6, 9, and 12, and brain ChE was determined for 5/sex/dose at termination of the study.

Ophthalmoscopic examinations were performed on all animals pretest, and at months 3, 6, 9, and 12 for Subgroup B. ERGs were performed for 5/sex/group at the same intervals. Fundus evaluations and retinal photographs were also done for selected high-dose and control animals. All animals had a gross examination at necropsy, with the exception of interim termination animals designated for perfusion. Electron microscopy of ocular tissues (optic nerve and retina) was performed on Subgroup B animals, and morphometric evaluations of teased nerve preparations were performed on selected animals of Subgroup A.

High-dose animals showed clinical signs of aggressiveness and hyperactivity. Reduced mean body weights occurred in both sexes at 50 ppm. Increased food consumption was noted in males at doses $\geq$ 2.5 ppm; the treatment relationship of this finding at 2.5 and 12.5 ppm is uncertain because of the absence of any effects on body weight. ChE (plasma, RBC, and brain) was inhibited in both sexes at 12.5 and 50 ppm; 2.5 ppm was an NOEL for cholinesterase inhibition.

No effects were seen at any dose on ophthalmological evaluations, ERG, retinal findings, eyes or optic nerve histopathology, or electron microscopy. (This contrasts with the increased incidence of retinal degeneration and cataracts observed in high-dose females in the two-year rat study.) This conclusion of the absence of treatment-related effects on the eye or optic nerves was supported by the study ophthalmologist in a supplementary document done to address EPA questions (Rubin, L. Evaluation of ERG data; submitted to EPA on January 4, 1994; no MRID assigned). EPA concurred with this conclusion in a DER of the supplementary eye and optic nerve document (OPP, 1996).

The original study pathologist (from Experimental Pathology Laboratories, EPL) concluded that effects on the sciatic nerve were present at doses $\geq$ 2.5 ppm with increased severity of findings at 50 ppm. The original EPA review concluded,

based on the data from evaluation of perfused rats provided by the EPL pathologist, that the NOEL for peripheral nerve lesions was 2.5 ppm. Statistical significance of findings was assessed by the EPA reviewer by combining data from males and females; however, there are biological reasons why this should not be done for sciatic nerve evaluations (chronic housing on wire-mesh bedding may damage the sciatic nerve; males are more susceptible to this damage due to their higher body weight).

The results of the Brennecke 1996 reevaluation of nerve tissue, which included *more* animals per dose group and was standardized in so far as possible for number and quality of the nerve tissue sections, failed to find any treatment-related effect on peripheral nerves (Brennecke, 1996, MRID 44204501, submitted to EPA on January 23, 1997).

EPA review of the Brennecke reevaluation of peripheral nerves from the 12-month rat study: Cheminova did not receive a review of the neuropathological reevaluation of the 12-month rat study until September 30, 1998, although the review was completed by EPA in September, 1997 (Raffaele, 1997). This delay on the part of EPA precluded any opportunity for Cheminova to develop a comprehensive rebuttal to the concerns expressed by the EPA reviewer.

EPA concluded that, based on the reevaluation, the NOEL for pathological effects on peripheral nerve tissue was 12.5 ppm. According to EPA's review, this conclusion is based partially on a highly equivocal increase in sciatic nerve lesions in 13-month males at 50 ppm. The EPA review actually states "the new evaluation shows no dose-related increase in either type of lesions in sciatic or tibial nerve, with the possible exception of the sciatic nerve in 13-month, 50 ppm males." There are no reasons given why 12-month and 13-month animals should be evaluated separately, and there is no biological basis for this procedure. As noted above, Cheminova concurs that males and females should be evaluated separately.

The data tabulated by EPA on page 4 of its review do not show a treatment-related effect on sciatic nerve in males; rather, there is a non-dose related pattern of a low incidence of minimal or mild “myelin bubbles” and “axonal degeneration” in all groups, including the control groups. (Male data as tabulated by EPA are shown below in Table B-14). However, on page 7 of the review, this “possible exception” is more strongly stated as an increase in lesions (without qualification) of the sciatic nerve in 13-month, 50 ppm males.” No basis was provided for the changed conclusion in the DER, and this conclusion is not supported by the study data.

Table B-14. Summary of Neuropathological Findings in Male Rats in the 12-Month Rat Study (Brennecke Findings as Tabulated by EPA Reviewer) (no quality assurance (QA) check has been made of the incidences)

Group (ppm)	Sciatic nerve		Tibial nerve	
	Myelin bubbles	Axonal degeneration	Myelin bubbles	Axonal degeneration
12-month				
0 (NP)	4 (1.5)	1 (1)	ne	ne
0	2 (1)	1 (1)	0 (0)	0 (0)
0.5	2 (1.5)	1 (1)	0 (0)	3 (1.3)
2.5	2 (2)	0 (0)	0 (0)	1 (1)
12.5	1 (1.5)	1 (1)	0 (0)	0 (0)
50	2 (1)	0 (0)	0 (0)	1 (1)
50 (NP)	1 (3)	1 (2)	ne	ne
13-month				
0	2 (1.5)	0 (0)	1 (1)	3 (1)
50	3 (2.3)	2 (1.5)	0 (0)	1 (1)

NP- not perfused
ne - not evaluated

EPA comments that the Brennecke 1996 reevaluation did not distinguish between perfused and unperfused tissues. Perfusion, if done correctly, may lead to a better quality of tissue for evaluation (it should also be noted that if not done correctly artifacts may result). However, the results of the reevaluation of the non-perfused tissues show that the slides from these animals provided an adequate basis for detection of peripheral nerve lesions, as lesions were characterized with generally similar incidence and severity in both the perfused and unperfused tissues. Thus, there did not appear to be any diminished sensitivity in the non-perfused tissues that would confound the evaluation, and tissues from perfused and non-perfused animals may be grouped for determining incidence of these specific lesions.

The EPA review of the reevaluation also indicates that "the findings of the current submission differ markedly from those of the original pathologist (EPL pathologist or Bio/dynamics pathologist)." Actually, review of the original study report shows that the Bio/dynamics pathologist (who evaluated tissues from non-perfused animals) failed to find an effect on the sciatic nerve at the high dose (thus tissues from non-perfused animals were not evaluated for the mid-or low-dose groups).

As discussed above, for perfused tissue direct comparison of findings on an animal by animal basis was not possible, because the EPL pathologist did not mark which tissue sections from each animal were chosen for evaluation (Multiple sections were on each slide). Because of this problem, EPA agreed prior to the reevaluation that a random sampling technique would be used, except for replacement when possible of sections compromised by poor quality.

The incidence of peripheral nerve findings in the Brennecke 1996 reevaluation is summarized in Table B-15. Note that the incidence includes both perfused and unperfused tissues and sums data from months 12 and 13. Incidences in males and females are reported separately, as is biologically appropriate.

**Table B-15. Summary of Histopathologic Findings—
Reevaluation of Peripheral Nerve Tissues From
Methyl Parathion Chronic (12-Month) Study**

Tissue/Lesion	Animals in Group With Lesions									
	0 ppm		0.5 ppm		2.5 ppm		12.5 ppm		50 ppm	
	M	F	M	F	M	F	M	F	M	F
Sciatic Nerve (number evaluated)	17	19	5	5	5	5	5	5	18	16
Myelin bubble, focal, minimal	5	4	1	1	—	1	1	—	2	4
Myelin bubble, multifocal, minimal	3	2	1	—	2	—	1	—	2	1
Myelin bubble, multifocal, mild	—	—	—	—	—	—	—	—	2	—
Axonal degeneration, focal, minimal	2	1	1	1	—	—	1	—	1	2
Axonal degeneration, multifocal, minimal	—	—	—	—	—	—	—	—	2	—
Inflammation, subacute, multifocal, minimal	—	—	—	—	—	—	—	—	1	—
Tibial Nerve (number evaluated)	10	10	5	5	5	5	5	5	10	9
Myelin bubble, focal, minimal	1	—	—	—	—	—	—	—	—	—
Axonal degeneration, focal, minimal	3	4	2	—	1	4	1	1	2	1
Axonal degeneration, multifocal, minimal	—	—	1	—	—	—	—	—	—	—
Total number of animals with lesions	12	9	3	2	3	4	4	1	8	6

It is apparent that there is no dose-response for either incidence or severity of the peripheral nerve lesions. Based on these data, the NOEL for effects on peripheral nerves in the one year rat chronic study with methyl parathion is 50 ppm (HDT). There is no evidence of cumulative neurotoxicity from exposure to methyl parathion in this study.

In addition, the reevaluation of peripheral nerve tissues in this study casts significant doubt on the conclusions regarding neuropathological effects from the two-year chronic study, particularly, the treatment relationship of findings at the low to mid dose levels. The 12-month study findings suggest that the chronic study findings would not be replicated if the chronic study had included evaluation of more animals, and (possibly) if the original chronic study evaluation had included a more standardized selection of nerve sections for evaluation.

The absence of treatment-relationship in the one-year rat study is also supported by the absence of treatment-related neuropathological lesions in the subchronic rat neurotoxicity study, which tested the same high dose of 50 ppm. The latter study included evaluation of longitudinal and cross-sections of peripheral nervous system tissues from perfused animals in the control and high-dose group, and, as discussed above, showed no treatment-related neuropathological effects.

Also supporting the conclusion that neuropathology is not a treatment-related consequence of low dose methyl parathion exposure, is the absence of evidence of neuropathology in the rat two-generation study [Bio/dynamics, 1982]. Although not including comprehensive neuropathological evaluations, this study did include histopathological evaluation of eyes (with optic nerve), brain, and sciatic nerve from 10 F_1 adults/sex/dose, and from F_1 and F_2 weanlings (5/sex/dose). The F_1 adults were exposed for 17 weeks prior to mating, through mating, gestation and lactation (6 to 8 weeks), and for a 5-week period post lactation at doses of 0, 0.5, 5.0 and 25.0 ppm. The F_1 and F_2 weanlings were exposed *in utero* and throughout lactation. There was no evidence of treatment-related histopathology in nervous system tissues in this study.

In its review of the reevaluation of the one-year rat study slides, EPA also states that the original study review (W.Sette to K.Swentzal) indicated that there was a treatment-related increase in demyelinated lengths in teased sural nerve preparations. The review of the Brennecke reevaluation also states that "The discussion in the current submission presents no new information which would alter our previous conclusions." Other than stating that the reviewing pathologist (i.e., Brennecke) concluded that the increases in demyelinated lengths are not biologically relevant, the EPA review fails to refute (or even disclose) the rationale provided by Brennecke as to why these slides should not be used for an assessment

of neuropathological sequelae. The rationale provided by Brennecke includes some key points:

- The data were very variable.
- No clear dose response was evident.
- There was no treatment-related decrease in the internodal length (which usually decreases markedly when degenerative changes are evident).
- Myelin ovoid formation was equivalent in the dosed groups and the controls (per the original pathologist).
- Even in the high-dose group animals the increased incidence of demyelinated fibers was only 4% of all teased nerve sections evaluated in the group.
- No historical control data are available for evaluating the significance of this finding.

The teased nerve preparations thus do not appear to provide a reliable basis for assessment of either a treatment-related effect or for determination of a NOEL.

Cheminova requested that Brennecke determine the necessity for re-evaluation of the teased nerve tissues. He recommended that the reevaluation not be conducted, based on a lack of treatment-relationship. It also should be noted that evaluation of teased nerve preparations is no longer done in standard neuropathological analyses, primarily due to high variability in the results.

As discussed above, a number of the procedural issues that were raised as concerns by the EPA reviewer of the reevaluation, e.g., the lack of a "blind" evaluation and the absence of a "peer review," had been discussed with EPA prior to the reevaluation being done and were agreed to by EPA. The reviewer was either unaware that this had been done or chose to ignore this fact. These procedural issues are cited by the EPA reviewer as a basis for concluding that the results of the original pathologist's evaluation still stand, that the NOEL for neuropathological effects is 2.5 ppm in this study (Sette, 1993), along with the reviewer's conclusion that an explanation for the differences in the results between the original pathologist and Brennecke's re-evaluation was not provided.

The uncertainty regarding the findings is not discussed by EPA in the HID document. It should be noted, however, that EPA states that ". . . previous reviews included evaluation of the neuropathology findings. Those evaluations resulted in

conflicting data interpretations leading to selection of different NOELs by different reviewers." In a memorandum from Swentzal to Schnaubelt (June 1993), Swentzal indicated that the "implications of the conclusions for the Core classification of the chronic toxicity/ carcinogenicity study cannot be determined until . . . the neurotoxicity data from *both studies* have been reviewed collectively (possibly by the peer review process) to determine a NOEL." Further, as discussed above, an additional EPA memorandum (Swentzal to Dumas, April 1996) indicated that due to a lack of consensus for a NOEL for neuropathology, OPP was not making a decision to upgrade the original chronic study. EPA stated that it would reevaluate *all existing data* including a sub-chronic neurotoxicity rat study (discussed above) to ascertain if a NOEL for neurotoxicity could be achieved.

There is no indication, however, that a comprehensive reevaluation of the neuropathological findings in the two chronic rat studies and the sub-chronic rat study was conducted by EPA. In fact, as noted above, the HID evaluation fails to even mention the existence of the one-year study, or the results of the Brennecke reevaluation of nervous system tissue from this study. Cheminova would like to discuss with EPA whether, and how, such a comprehensive evaluation should be conducted. Cheminova believes in the interim that EPA should clearly identify the uncertainties regarding treatment-related neuropathology in these studies.

In conclusion, there is no overt neuropathological effect at low dose levels in any of these studies. It is clear from all available rat studies that 50 ppm is a highly toxic dose to rats, with significant behavioral effects, brain and RBC cholinesterase inhibition, and retinal degeneration in females (after two years, but not after one year exposure). But even at this high dose level the evidence for treatment-related effects on peripheral nerves is equivocal, with mixed results between studies.

IV. ENDPOINT SELECTION

Cheminova believes that endpoint selection in the HID document for methyl parathion is questionable and fails to adequately consider the impact of exposure route, high dose to low dose extrapolation, and the likely dermal absorption of methyl parathion

A. REFERENCE DOSE FOR ORAL EXPOSURE

In selection of an endpoint for development of an RfD for chronic dietary exposure, EPA considered only the Daly et. al. (1983) chronic two-year rat study, and failed to consider the results of either the subchronic neurotoxicity rat study (Minnema, 1994b) or the 12-month chronic rat study (Daly, 1991). As noted previously, the 2-year study has some limitations that should be considered before relying solely on this study for developing an RfD. Among these limitations are

that the number of animals evaluated for neuropathological findings in the 2-year chronic rat study is not adequate to define an NOEL for peripheral nerve effects, and that the high incidence of intercurrent infection in this study may have compromised the chronic toxicity evaluation. Further, as discussed in the review of the chronic rat study (Section III C) , Cheminova does not agree with the NOEL of 0.02 mg/kg bw/day determined by EPA from this study. Cheminova believes that 0.2 mg/kg bw/day is a NOAEL dose in this study.

As discussed previously in Section III D, EPA memoranda reviewing the chronic rat studies have discussed the need for a peer review for characterization of the NOEL for methyl parathion neurotoxicity. Cheminova agrees this would be appropriate, particularly as a reevaluation of nervous system tissues (Brennecke, 1996) from the 12-month chronic study showed no treatment-related peripheral nerve lesions at any dose. Cheminova would like to discuss with the Agency whether and how such an evaluation should be conducted.

The Toxicology Endpoint Selection Process guidance developed by EPA (Rowland, 1997) indicates the following:

> A dose should not be selected routinely [as the NOEL] by default simply because it is the NOEL. The entire dose response curve should be reviewed to determine how the NOEL relates to the dose at which effects actually begin to appear (i.e., the LOEL). In some cases, data from two studies may be considered together to determine the most appropriate NOEL.

Cheminova followed this approach and evaluated all three of the longer-term rat studies that included neuropathological evaluations. Based on this evaluation, Cheminova believes the NOEL of 0.11 mg/kg bw/day derived from the rat chronic study is reasonable to use as a chronic study NOAEL for deriving an RfD. Results of the three longer-term rat studies that included neuropathological evaluations are summarized in Table B-16 below.

Table B-16. Summary of Subchronic and Chronic Studies in Rats with Methyl Parathion

Study Effects	LOEL	NOAEL ppm (mg/kg/day)
Subchronic neurotoxicity (Minnema, 1994b)		
- neurobehavioral signs	50 ppm	5 ppm (0.31M;0.37 F)
- brain ChE inhibition	50 ppm	5 ppm (0.31M; 0.37F)
- neuropathology	No effect	50 ppm (3.12M;4.05F) (HDT)
-RBC cholinesterase inhibition	5 ppm (marginal)	0.5 ppm (0.03M; 0.04F)—because of the marginal nature of the RBC findings and the absence of other effects at this dose; Cheminova is proposing 0.1 mg/kg/day as an NOAEL
-hematological effects	not evaluated	
One-year chronic (Daly, 1991)		
- neurobehavioral signs	50 ppm	12.5 ppm (0.53M; 0.70F)
- brain ChE inhibition	12.5 ppm	2.5 ppm (0.11M;0.14F)
- neuropathology based on reevaluation	No effect	50 ppm (2.2M;3.1F) (HDT)
- retinal degeneration or ocular effects	No effect	50 ppm (2.2M;3.1F) (HDT)
- RBC cholinesterase inhibition	12.5 ppm	2.5 ppm (0.11M;0.14F)
- hematological effects	not evaluated	
Two year chronic (Daly and Hogan, 1983)		
- neurobehavioral signs	50 ppm	5 ppm (0.21M;0.29F)
- brain ChE inhibition	50 ppm	5 ppm (0.21M;0.29F)
- neuropathology (equivocal, M only)	50 ppm	5 ppm (0.21M;0.29F)
- retinal degeneration	50 ppm	5 ppm (0.21M;0.29F)—less than 20% inhibition; not statistically significant
- RBC cholinesterase inhibition	50 ppm	
- hematologic effects	50 ppm	5 ppm (0.21M;0.29F)—very slight findings at this dose; within normal range for older animals

Good concordance is shown for the results of these studies for most of the parameters evaluated, and 0.11 mg/kg bw/day from the 1-year rat study is a conservative choice for an overall chronic NOAEL. This study was selected for NOEL derivation in lieu of the 2-year study because of the inadequate neuropathological evaluations in the 2-year study and because of the high rate of intercurrent infection in the 2- year study, which may have confounded the systemic toxicity evaluation.

That an NOAEL of 0.11 mg/kg bw/day is conservative for intermediate to longer term exposures to methyl parathion is also supported by a human 30-day oral study of methyl parathion, which showed an NOEL of 0.31 mg/kg bw/day for plasma and RBC cholinesterase inhibition (Rider et al., 1971). Although this is an older study with some deficiencies and limited reporting, the study design appears basically sound for evaluating potential effects on cholinesterase in humans. EPA, in fact, used the human study as the basis in setting a drinking water Health Advisory for methyl parathion in 1988 (Office of Drinking Water, 1988). Although Cheminova believes that the available data from this study are too limited to use exclusively as a basis for risk assessment, the study results provide assurance that the animal study results are not under-predicting toxicity to humans.

Additionally, for the reasons detailed in this document and in Appendix A, Cheminova does not believe that retention of the FQPA 10X safety factor is appropriate for methyl parathion.

B. ACUTE EXPOSURE

As discussed previously, choosing the NOEL from the acute gavage neurotoxicity study for estimation of acute dietary risk is overly conservative due to the study objective to characterize neurotoxic potential at high doses.

Cheminova is currently developing additional acute dietary data, including neuropathological evaluations, to determine the acute NOEL dose.

Cheminova believes in the interim it is appropriate to follow the procedure outlined by Rowland, 1977, as described above, for establishing a NOEL for acute exposure.

Because the endpoint of concern is neuropathological changes, which would not be expected to be reversible, the subchronic neurotoxicity study (Minnema, 1994b) provides useful results which may be used in conjunction with the acute study to determine an acute NOEL.

The data from this subchronic study provide support for a hypothesis that an acute *dietary* dose of 0.3 mg/kg would not likely show any adverse clinical signs or significant inhibition of RBC or brain cholinesterase and that up to 10-fold greater acute dietary exposures would not be likely to lead to any adverse irreversible neurobehavioral effects or neuropathological findings. These estimated acute NOELs are based on mean compound consumption in the subchronic study and are therefore conservative. Actual daily compound intake on a per body weight basis during the first two weeks of the subchronic study was significantly higher than mean consumption during the entire 13-week study, as may be seen in the bar graphs attached to this document (Attachment I).

Cheminova recommends that the subchronic neurotoxicity data be taken into consideration for establishing an NOEL for acute dietary exposure, and that 0.3 mg/kg be used as a surrogate NOEL for acute dietary risk calculation until additional acute data are developed.

C. SHORT-TERM EXPOSURE

EPA is proposing use of the NOEL from the gavage acute neurotoxicity study for endpoint selection for short-term exposure situations.

Cheminova is currently conducting a study, including neuropathological assessment, to better define the NOEL for neurotoxicity following short-term (1-5 day) dermal exposure.

Cheminova recommends that the subchronic neurotoxicity study (Minnema, 1994) be used to derive an interim NOAEL for short-term risk assessment. The dietary route of the subchronic neurotoxicity study provides a time course of exposure more similar to short-term occupational exposure, than does a bolus acute dose. (Residential exposure to methyl parathion is precluded by label restrictions, so the only dermal exposure scenario of concern is occupational.) Additionally, the longer duration of the subchronic study makes deriving the NOAEL from this study a conservative decision. This study showed an NOEL for neurobehavioral effects and for inhibition of brain cholinesterase at 5 ppm (approximately 0.3 mg/kg bw/day), and an NOEL for neuropathological findings at 50 ppm (HDT). RBC cholinesterase inhibition was seen at the 0.3 mg/kg bw/day dose level; however, Cheminova believes that this dose level is extremely close to an NOAEL for subchronic exposure to methyl parathion. This conclusion is supported by the absence at 0.3 mg/kg bw/day of behavioral effects or clinical signs of toxicity, which were evaluated in this study much more rigorously and systematically than in a standard subchronic study. Cheminova considers this dose level a low-effect-level (LEL), however, an appropriate conservative extrapolation

would set the NOEL using a 3-fold factor, i.e., to 0.1 mg/kg bw/day rather than using the ten-fold lower low dose as the NOEL.

In the memorandum titled "Methyl Parathion. The HED Chapter of the Reregistration Eligibility Decision Document (RED)" (Diane Locke, September 1, 1998), the Agency notes that per an EPA policy decision, the FQPA Safety Factor will not be retained for any occupational risk assessments for pesticides. Cheminova concurs with this conclusion, although, as noted previously, Cheminova does not believe retention of this factor is necessary for methyl parathion.

D. INTERMEDIATE-TERM EXPOSURE

EPA is proposing use of the rat chronic study for this endpoint. The subchronic neurotoxicity study provides a time frame that is more relevant to intermediate-term occupational exposure to methyl parathion (as indicated above, residential exposure is precluded) than does the chronic feeding study. The subchronic study also included specific test parameters to more completely characterize neurotoxicity and more detailed neuropathological evaluations. The time frame of the subchronic study also more closely approximates an intermediate-term exposure. Further, the complete characterization of neurotoxicity, including FOB and motor activity evaluations, evaluation of cholinesterase in six different brain regions, and detailed neuropathology, all argue that this study is more suitable for assessing of intermediate exposure than is the chronic rat study.

In its comments supporting the selection of the two-year chronic study for this endpoint EPA indicates that there is "evidence of cumulative neurotoxic effects" (page 19 of the HID document). For the reasons developed earlier, Cheminova believes that a weight-of-the-evidence evaluation of results from the subchronic neurotoxicity study, the 12-month special eye and nerve study, and, considering its limitations, the 2-year chronic rat study, fails to support a determination that cumulative neurotoxicity occurs from exposure to methyl parathion.

Therefore, Cheminova recommends that the subchronic neurotoxicity study results be used to assess the potential risks from intermediate-term exposure.. The subchronic study results are discussed above, under "short term exposure." A conservative extrapolation from these study data would set the NOEL using a 3-fold factor, i.e., to 0.1 mg/kg bw/day. Cheminova agrees with EPA's decision not to retain the additional FQPA 10x safety factor for intermediate term occupational exposures.

E. CHRONIC EXPOSURE

EPA is proposing to use the chronic 2-year study of methyl parathion as the basis for *chronic* occupational risk assessment. Cheminova disagrees with this selection, for the same reasons described above that show this study should not be the sole basis for a chronic RfD. Cheminova agrees with EPA's decision not to retain the additional FQPA 10x safety factor for chronic occupational exposures.

F. INHALATION EXPOSURE

EPA is proposing to use the chronic 2-year study of methyl parathion as the basis for risk assessment from any inhalation exposure. Cheminova has several concerns regarding EPA's conclusions in this area.

- First, it is not appropriate to select an NOEL from a chronic study as the basis for risk assessment for acute and intermediate exposures as well as for long-term exposures. Endpoints from studies of the appropriate duration should be selected for each different exposure scenario.

- Second, both occupational and ambient exposures to methyl parathion may be reasonably expected to be seasonal with occasional acute peaks, rather than chronic. This conclusion is supported by the seasonal use patterns for methyl parathion, and the rapid degradation of this compound in air. Cheminova suggests that either the subchronic neurotoxicity study (NOEL of 0.1 mg/kg bw/day) or the rat one-year chronic study (NOEL of 0.11 mg/kg bw/day) would provide more appropriate choices for risk assessment (depending on the duration of the exposure in question).

- Third, to reiterate, EPA states that the additional FQPA 10x safety factor would not be retained for occupational exposures. Cheminova agrees with this policy decision by EPA regarding occupational exposures, although Cheminova does not agree that the 10X factor should be retained for any risk calculation for methyl parathion, as discussed above.

G. ESTIMATE OF DERMAL ABSORPTION

EPA is proposing a 100% default for dermal absorption, based on the lack of confidence by the Agency in a much lower percentage of dermal absorption predicted based on a 21-day rabbit dermal study of methyl parathion (Goad, 1992; MRID 42263701).

A 100% default is overly conservative. EPA appears to base the default on the absence of a "valid" dermal study, and on one set of LD_{50} data which shows similar LD_{50}s for oral and dermal administration. However, it is not known whether oral exposure to the test material was precluded in the dermal LD_{50} study included in the HID review. There are other data that may be used to more accurately estimate dermal absorption. For example, as shown in Table B-17 and Table B-18, a comparison of rat dermal and oral LD_{50} data for both the technical product and the emulsifiable concentrate formulation developed by shows at least a 10-fold difference in lethality between oral and dermal routes. The Safepharm acute study reports used as the basis for this table are being submitted to EPA.

Table B-17. Comparison of Acute LD_{50}s for Oral and Dermal Application to Rats

Year	Report No.	Formu l-ation	% a.i.	Laboratory	Rat Strain	Route	Vehicle	Dose (mg/kg)	
								Male	Female
1993	545/7	EC	47.1	SafePharm	S-D	Oral	Distilled Water	10; 16; 25; 63	10; 16; 25; 63
1993	545/8	EC	47.1	SafePharm	S-D	Dermal	Distilled Water	500; 1,000; 2,000	500; 1,000; 2,000
1986	34117/ 34	TC	79.2	IRI	S-D	Oral	Corn Oil	20; 30; 40	40; 70; 100
1986	34117/ 34	TC	79.2	IRI	S-D	Dermal	None	400; 500; 600	400; 500; 600

Table B-18. Comparison of Acute LD_{50}s for Oral and Dermal Application to Rats

Year	Report No.	Dosing Volume		Males			Females			Method for LD_{50} Calculation
				LD_{50} mg/kg b.w.			LD_{50} mg/kg b.w.			
		Route	ml/kg b.w.	LD_{50}	>	<	LD_{50}	>	<	
1993	545/7	Oral	10.0	33	23	48	28	18	43	Dreher
1993	545/8	Dermal	10.0	561	232	1,360	1,682	1,091	2,594	Dreher
1986	34117/ 34	Oral	10.0	25	21	30	62	47	82	Cuthbert; Carr
1986	34117/ 34	Dermal	—	483	427	546	481	437	529	Cuthbert; Carr

EC = emulsifiable concentrate
TC = technical product
a.i. = active ingredient

From the data in Tables 17 and 18, one can conclude that for either the technical concentrate or the EC formulation, the dermal LD_{50} is at least 10 times the oral LD_{50}. Thus, for dermal exposure a dermal absorption factor of 10% should be sufficient. This is protective of humans because rat skin is more permeable than human skin for the majority of compounds tested.

Further, *in vitro* studies using rat skin under worst-case occlusive conditions predict that dermal penetration of methyl parathion does not exceed 25%. Confidence in these *in vitro* data is limited due to the variability of the results; however, the data clearly show, in conjunction with the acute oral and dermal study data, that the extent of dermal penetration of methyl parathion would not approach 100% of the applied dose.

Thus, a default absorption of 10% to 25% provides a more justifiable estimate of dermal penetration in rats than the 100% default used by EPA. These data also correlate with dermal penetration estimates developed for the closely structurally related compound ethyl parathion. It should be noted that Cheminova is currently developing dermal study data to more clearly define the NOELs for cholinesterase inhibition, clinical signs and potential neuropathology from short-term duration dermal exposures.

V. CONCLUSION

Available data on methyl parathion do not support the addition of an extra 10-fold safety factor to account for the potential sensitivity of young compared with adults, based on the following:

- a lack of unique fetal or pup susceptibility to methyl parathion in Guideline reproductive and developmental toxicity studies;

- a lack of credible evidence of increased fetal or pup susceptibility at doses or by routes relevant to potential human exposure in the published literature; and

- a lack of evidence of irreversible neurotoxicological effects in pups or adults at low doses.

The absence of a developmental neurotoxicity study should not be used by EPA as the basis for an additional safety factor because the study has never been requested or required for methyl parathion by EPA and because there is no evidence that methyl parathion poses a specific developmental neurotoxic hazard.

The study and endpoint selection proposed for risk assessment in the HID document is questionable based on the following:

- In selecting an *RfD* for assessing the risks potentially associated with *chronic* exposure to methyl parathion, EPA considered only the Daly, 1991 chronic (two-year) rat study. Based on a weight-of the evidence evaluation, Cheminova believes that an NOAEL derived from all three longer term methyl parathion rat studies provides a conservative value for deriving the RfD. Additionally, for the reasons detailed in this document and in Appendix A, Cheminova does not believe that retention of the FQPA 10x safety factor is appropriate for methyl parathion.

- EPA is proposing to use the acute neurotoxicity study NOEL for *acute* dietary risk assessment and for assessment of risks from *short-term* occupational exposure situations. This is overly conservative because the acute study objective was to characterize neurotoxic potential at high doses and because the gavage route of administration was used. Data from the dietary subchronic neurotoxicity study provide a conservative and more justifiable basis for predicting an NOEL to evaluate potential risk from acute dietary exposure or from short-term dermal exposure situations, until additional acute dietary and short-term dermal data are developed for use in risk assessments.

- EPA is proposing to use the chronic two-year study of methyl parathion as the basis for *intermediate*-term risk assessment. The subchronic neurotoxicity study provides a more realistic exposure scenario for estimation of risks potentially associated with intermediate-term exposure than does the chronic study.

- EPA is proposing to use the chronic two year study of methyl parathion as the basis for *chronic* risk assessment. Cheminova believes this approach is flawed, for the same reasons Cheminova believes the use of this study as the sole basis for the RfD is inappropriate.

- EPA is proposing to use the chronic two year study of methyl parathion as the basis for risk assessment from inhalation exposure of any duration. Cheminova believes that studies of the appropriate duration should be selected for evaluating inhalation risks under different exposure scenarios.

- EPA is proposing a 100% default for dermal absorption to use in assessing the risks associated with dermal exposure (extrapolating from oral toxicity data). Other data should be used to more accurately estimate dermal absorption; these data predict dermal absorption for methyl parathion to be between 10% to 25%.

APPENDIX B

FIGURE B-1: TEST MATERIAL CONSUMPTION (MALES, O.5 ppm)

Subchronic Neurotoxicity Study of Dietary MP3 In Rats (#200 -MP3)
Minnema, 1994b (MRID 43490501)

FIGURE B-2: TEST MATERIAL CONSUMPTION (FEMALES, 0.5 ppm)

Subchronic Neurotoxicity Study of Dietary MP3 In Rats (#200 -MP3)
Minnema, 1994b (MRID 43490501)

FIGURE B-3: TEST MATERIAL CONSUMPTION (MALES, 5.0 ppm)

Subchronic Neurotoxicity Study of Dietary MP3 In Rats (#200 -MP3)
Minnema, 1994b (MRID 43490501)

FIGURE B-4: TEST MATERIAL CONSUMPTION (FEMALES, 5.0 ppm)

Subchronic Neurotoxicity Study of Dietary MP3 In Rats (#200 -MP3)
Minnema, 1994b (MRID 43490501)

FIGURE B-5: TEST MATERIAL CONSUMPTION (MALES, 50.0 ppm)

Subchronic Neurotoxicity Study of Dietary MP3 In Rats (#200 -MP3)
Minnema, 1994b (MRID 43490501)

FIGURE B-6: TEST MATERIAL CONSUMPTION (FEMALES, 50.0 ppm)

Subchronic Neurotoxicity Study of Dietary MP3 In Rats (#200 -MP3)
Minnema, 1994b (MRID 43490501)

TABLE B-19: TEST MATERIAL CONSUMPTION VALUES (0.5 ppm)

Subchronic Neurotoxicity Study of Dietary MP3 In Rats (#200 -MP3)
Minnema, 1994b (MRID 43490501)

Test Substance Intake, Males 0.5 ppm			
Week	**Weight**	**Food Cons**	**mg/kg bw/d**
1	272	190	0.0499
2	326	196	0.0429
3	368	185	0.0359
4	405	178	0.0314
5	433	183	0.0302
6	461	193	0.0299
7	489	189	0.0276
8	509	187	0.0262
9	523	183	0.0250
10	539	186	0.0246
11	555	182	0.0234
12	564	181	0.0229
13	577	184	0.0228
		Mean	**0.0302**

Test Substance Intake, Females 0.5 ppm			
Week	**Weight**	**Food Cons**	**mg/kg bw/d**
1	171	130	0.0543
2	193	140	0.0518
3	214	139	0.0464
4	232	128	0.0394
5	245	132	0.0385
6	255	138	0.0387
7	264	135	0.0365
8	274	127	0.0331
9	278	127	0.0326

10	281	130	0.0330
11	288	123	0.0305
12	291	126	0.0309
13	298	114	0.0273
		Mean	**0.0379**

TABLE B-20: TEST MATERIAL CONSUMPTION VALUES (5.0 ppm)

Subchronic Neurotoxicity Study Of Dietary MP3 In Rats (#200 -MP3)
Minnema, 1994b (MRID 43490501)

Test Substance Intake, Males 5.0 ppm			
Week	**Weight**	**Food Cons**	**mg/kg bw/d**
1	272	182	0.478
2	323	197	0.436
3	368	191	0.371
4	405	178	0.314
5	432	191	0.316
6	460	196	0.304
7	491	191	0.278
8	514	191	0.265
9	526	192	0.261
10	544	196	0.257
11	561	185	0.236
12	570	183	0.229
13	580	190	0.234
		Mean	**0.306**

Test Substance Intake, Females 5.0 ppm			
Week	**Weight**	**Food Cons**	**mg/kg bw/d**
1	171	130	0.543
2	32193	138	0.511
3	215	132	0.436
4	229	123	0.384
5	243	127	0.373
6	253	129	0.364
7	256	129	0.360
8	273	127	0.332
9	280	131	0.334

10	287	131	0.326
11	291	130	0.319
12	296	129	0.311
13	305	116	0.272
		Mean	**0.374**

TABLE B-21: TEST MATERIAL CONSUMPTION VALUES (50 ppm)

Subchronic Neurotoxicity Study Of Dietary MP3 In Rats (#200 -MP3)
Minnema, 1994b (MRID 43490501)

Test Substance Intake, Males 50 ppm			
Week	**Weight**	**Food Cons**	**mg/kg bw/d**
1	268	174	4.638
2	309	175	4.045
3	343	174	3.623
4	378	174	3.288
5	406	193	3.395
6	425	197	3.311
7	447	183	2.924
8	469	186	2.833
9	490	179	2.609
10	505	182	2.574
11	521	183	2.509
12	527	185	2.507
13	538	174	2.310
		Mean	**3.121**

Test Substance Intake, Females 50 ppm			
Week	**Weight**	**Food Cons**	**mg/kg bw/d**
1	175	118	4.816
2	183	114	4.450
3	196	125	4.555
4	210	134	4.558
5	227	148	4.657
6	239	148	4.423
7	247	145	4.193
8	264	142	3.842
9	268	132	3.518

10	275	137	3.558
11	279	136	3.482
12	284	135	3.395
13	287	127	3.161
		Mean	**4.047**

Attachment C

Comments on EPA's Hazard Assessment of the Organophosphates and FQPA Safety Factor Recommendations for the Organophosphates

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8 pages

I. INTRODUCTION

These comments, submitted by Cheminova Agro A/S (Cheminova), concern a July 7, 1998, draft report from EPA's Hazard Identification Assessment Review Committee (HIARC) titled *Hazard Assessment of the Organophosphates* (herein referred to as the "Hazard Report "), and an August 6, 1998, combined report from the Food Quality Protection Act (FQPA) Safety Factor Committee and the HIARC, titled *FQPA Safety Factor Recommendations for the Organophosphates* (herein referred to as the "Safety Factor Report"). In these comments, Cheminova highlights several inconsistencies between EPA's conclusions on methyl parathion and its conclusions on other organophosphates and identifies errors in both of these reports with regard to methyl parathion. Further, in these comments Cheminova addresses issues or data requirements newly raised for methyl parathion in the Hazard Report that were not included in a December 1, 1997, Hazard Identification (HID) Committee report on methyl parathion (herein referred to as the "HID document") or in the March 10, 1998, Toxicology Chapter for methyl parathion. (Note: Cheminova's comments on the methyl parathion HID document are included in Attachment B; comments on the Toxicology Chapter are included in Attachment A.)

II. NEUROPATHOLOGY

EPA Conclusion: EPA uses evidence of neuropathology "at low doses" as part of the bases substantiating retention of the FQPA safety factor and for requiring a developmental neurotoxicity study. Neuropathology is discussed in the Hazard Report in the following sections: (1) evaluation of neurotoxicity (page 2); (2) tabulated summary for methyl parathion (page 19); and (3) rationale for retaining the 10X FQPA safety factor for methyl parathion (page 34). The topic is discussed in the Safety Factor Report on pages 4 and 17.

Cheminova Comments: A weight-of-the-evidence evaluation of the results of rat toxicity studies casts significant doubt on the treatment relationship of the neuropathological lesions, with the exception of lesions seen in an acute gavage study at doses exceeding a lethal dose 50% (LD_{50}) and, possibly in a 2-year study at a markedly toxic dose level (50 ppm or approximately 2.5 mg/kg/day).

Neither of the EPA documents included results from the most recent neuropathological evaluation for methyl parathion (reevaluation of nerve tissues from the 12-month rat study (Brennecke, 1996)), which showed no treatment-related neuropathological lesions at doses up to the highest dose tested (HDT) of 50 ppm. As discussed in detail in Cheminova's comments on the HID document (Attachment B), EPA chose to ignore these results rather than to include them in a weight-of-the-evidence evaluation. EPA did so primarily on the grounds that the reevaluation used improper procedures,

even though Cheminova representatives had discussed these issues with EPA staff and obtained EPA acceptance of the procedures to be used in the reevaluation before it was performed.

The results of the Brennecke reevaluation also call into question the treatment relationship of the low- and mid-dose findings in the 2-year chronic rat study. The 12-month study was conducted in part to address questions concerning the NOEL for sciatic nerve effects in the 2-year study. The 2-year study is difficult to evaluate because of the small numbers of animals for which nerves were evaluated and the normal high background incidence of sciatic nerve lesions in older male rats maintained in wire mesh caging.

As discussed in the overview document, Cheminova is recommending using data from all three of the longer term rat studies of methyl parathion that included neuropathological evaluation to set a chronic NOEL, until a full peer review evaluation of all three studies can be performed to provide an adequate basis for determining whether a neuropathological effect exists, and if it does, at what doses.

The evaluation of neurotoxicity summarized on page 2 of the Hazard Report and the rationale for retaining the 10X FQPA safety factor for methyl parathion on page 34 of the Safety Factor Report indicate that treatment-related neuropathology was observed in the subchronic neurotoxicity study of methyl parathion. On the other hand, the HID document and the tabulated summary for methyl parathion on page 19 of the Hazard Report refer to the subchronic neurotoxicity study histopathological findings as "equivocal." The EPA data evaluation record for this study (Office of Pesticide Programs, 1996) concluded unequivocally that there were no treatment-related neuropathological effects (as does the review of the study on page 13 included in the Health Effects Division (HED) Reregistration Eligibility Document (RED) chapter). This finding concurs with that of the study director, the study pathologist, and Cheminova. EPA has provided no rationale to support the change in its conclusions. As indicated in the comments regarding the HID document (Attachment B), Cheminova believes that these data do not support a conclusion that neuropathological lesions resulted from methyl parathion dietary exposures at any dose level in the subchronic neurotoxicity study.

The Hazard Report also fails to indicate that unequivocally treatment-related neuropathological findings in the methyl parathion acute neurotoxicity study were seen only at the high (and lethal) dose levels. Equivocal effects were seen in the mid-dose males, but even the mid-dose level was severely toxic and exceeded the oral LD_{50} cited by EPA in the Toxicology Chapter.

In contrast to the approach taken for methyl parathion, the Hazard Report 's discussion of evidence of delayed neuropathy for chlorpyrifos and methamidaphos indicates that evidence was seen "at lethal doses" or "at extremely high dose levels (greatly in excess of the hen LD_{50})." Cheminova believes it is appropriate to evaluate the significance of neuropathological findings (whether related to delayed neuropathy or not) in the context of overall systemic toxicity, and it believes this approach should also be followed for methyl parathion. Neuropathological changes of minimal severity seen only at lethal dose levels should not provide a basis for any additional concern for effects from low dose exposures to a compound.

Organophosphate-induced delayed neuropathy (OPIDN) is not discussed in the HID document for methyl parathion and is only briefly discussed in the Toxicology Chapter, but it is included as a significant topic in the Hazard Report and the Safety Factor Report. The textual evaluations of neurotoxicity in the latter documents fail to indicate that an acceptable delayed neurotoxicity hen study conducted with methyl parathion was negative for any evidence of OPIDN. (This fact is noted, however, in the tabulated summary on page 19 of the Hazard Report .) It should be discussed in the context of the overall neurotoxicity evaluation because methyl parathion is the only organophosphate (OP) that is not associated with OPIDN but that is nonetheless included in the neuropathology discussion section of these documents. Cheminova questions the basis for grouping methyl parathion with the OPIDN-inducing organophosphate chemicals and the blurring of a distinction between any type of neuropathological findings and those characteristic of OPIDN.

OPIDN may occur in the absence of evidence of cholinesterase (ChE) inhibition; and because it is a delayed phenomenon, there may be no warning signs that allow effective preventive measures. Thus, it is one of the most feared potential consequences of exposure to some OP chemicals and merits a high degree of concern. As discussed above, methyl parathion was negative for OPIDN in an acceptable test in a species (hen) known to be susceptible to OPIDN.

The confusion of histopathological findings is exacerbated in the Safety Factor Report's discussion of chlorpyrifos and methyl parathion on page 17. It states: "Specifically for Chlorpyrifos and Methyl Parathion, in studies conducted at various scientific laboratories and reported in the open literature, neuropathology was observed in animals and/or humans, and evidence of . . ." Cheminova is not aware of any studies published in the open literature that show neuropathology resulting from exposure to methyl parathion in animals, nor is it aware of any studies showing neuropathology from exposure to methyl parathion in humans. Chlorpyrifos has been reported to be potentially associated with OPIDN in animals and humans at high dose levels, but no evidence of OPIDN has been seen in methyl parathion studies. The neuropathological findings for methyl parathion in the acute neurotoxicity study are not characteristic of delayed neuropathy, based on lesion characteristics, minimal

degree of severity, early time of onset, and lack of persistent functional correlates, that is, compromised neuromuscular activity.

EPA indicates that the presence of neuropathology in adult animals may be indicative of enhanced susceptibility of the developing nervous system (Hazard Report, page 1, and Safety Factor Report, page 2). Cheminova is not aware of any data showing a positive correlation between the potential of a compound to induce nervous tissue lesions in adults and enhanced toxicity to the developing nervous system in young. Immature animals may actually be less vulnerable to certain types of nervous system damage because of enhanced plasticity and repair capacity compared with mature animals. For example, chicks and immature animals are less susceptible to OPIDN than are adult animals (Abou-Donia, 1981). Neuropathological findings, particularly if seen following low dose exposures, raise concern regarding potential effects in either adults or young, but in and of themselves do not predict any special susceptibility of the developing organism. Further, the neuropathology seen in the chronic study, even if treatment-related, is not relevant to assessing the potential for developmental toxicity (or developmental neurotoxicity), because the time frame for the chronic study far exceeds the time frame of any developmental stage. The effects seen in the acute study at doses in excess of the LD_{50} are also not relevant to any human exposure scenario other than intentional poisoning. Therefore, the neuropathology seen in the case of methyl parathion does not support a particular concern for developmental neurotoxicity.

III. NEUROTOXIC ESTERASE (NTE) REQUIREMENT

EPA Conclusion: The Safety Factor report (page 4) indicates, for methyl parathion among other OP chemicals, that "a study that evaluates the effects on the neurotoxic esterase (NTE) is necessary . . . The lack of NTE data in an otherwise acceptable negative hen study is not considered a major data gap, but indicates a need for confirmatory data (i.e., data to confirm that an effect on NTE does not occur)." This requirement is not included in the HID document or in the Toxicology Chapter document for methyl parathion.

Cheminova Comments: Cheminova does not consider that an NTE "confirmatory" assay should be required for methyl parathion for the following reasons:

- In an acute hen neurotoxicity study that was considered acceptable by EPA, methyl parathion did not show clinical signs or neuropathology indicative of OPIDN (Beavers et al., 1990).

- A hen delayed neurotoxicity study published in the open literature included NTE evaluation following a single oral dose of 100 mg/kg methyl parathion (followed

by atropine as needed). This study found only 12 % inhibition of NTE and no evidence of OPIDN at a dose level causing severe brain ChE inhibition (85% decrease compared to control) (Ohkawa et al., 1980).

- Ethyl parathion, which is a close structural analogue of methyl parathion, has been used as a negative control in multiple assays for OPIDN, and its potential for NTE inhibition has been evaluated in subchronic oral and dermal hen studies. No significant NTE inhibition resulted from ethyl parathion exposures at a maximum tolerated dose (MTD) in hens (Soliman et al., 1982).

- NTE assay results are inherently variable and have a high standard deviation. It is not technically sound to conduct an NTE assay in isolation from evaluation of other indicators of OPIDN.

- NTE inhibition, by itself, is not necessarily predictive of OPIDN potential. Some carbamates, phosphinates, and several dimethyl phosphates inhibit NTE but produce no signs of OPIDN (Abou-Donia, 1981).

- In the absence of clinical signs or neuropathological findings of OPIDN, NTE inhibition cannot be used to "confirm" the presence or absence of OPIDN.

Thus, Cheminova believes no "confirmatory" NTE analyses should be required.

IV. EVIDENCE OF INCREASED SUSCEPTIBILITY OF DEVELOPING ORGANISMS TO METHYL PARATHION

EPA Conclusion: EPA concludes that there is evidence of increased susceptibility to methyl parathion, based on the presence of neuropathology and on published studies in the literature that purport to show increased susceptibility.

Cheminova Comments: The weakness of the evidence of increased susceptibility to methyl parathion for fetuses or pups and the lack of relevance of the published data to human risk assessment are discussed at length in Attachment B (Cheminova's comments on the HID document). Several specific points in the Hazard Report and the Safety Factor Report should be corrected.

The Hazard Report and the Safety Factor Report rely on the evidence of neuropathology in adult animals as evidence of increased susceptibility of developing organisms to methyl parathion. As noted above (Neuropathology section), Cheminova is not aware of any data supporting a correlation between neuropathological findings in adult animals and an increased susceptibility of the developing nervous system. The nature of effects in adult animals should not be used as a basis for retaining the 10X

safety factor unless (a) those effects strongly point toward unassessed developmental effects in infants or children, or (b) effects in offspring also have been characterized and the offspring are more susceptible. Developmental toxicity studies with methyl parathion have not shown abnormalities in the development of the fetal nervous system even at high doses markedly toxic to the adult animals. See the discussion of this topic in the June 1998 IWG Issue Paper entitled *The FQPA Additional Uncertainty Factor*.

The Hazard Report (page 34) (point three of "rationale for retaining the 10X FQPA safety factor") indicates that open literature data for chlorpyrifos also demonstrated differences in susceptibility of the offspring. It is not clear why chlorpyrifos data are referenced in the context of an evaluation of methyl parathion or why these data are considered relevant to an assessment of methyl parathion. Chlorpyrifos and methyl parathion are different structurally, and their pattern of toxicity differs. Assessments of other OPs in the Hazard Report do not mention chlorpyrifos data as evidence for increased susceptibility to a different organophosphate.

Page 4 of the Hazard Report and page 6 of the Safety Factor Report, under the subheading of prenatal developmental toxicity studies in rats, indicate that "in pre/post-natal studies published in the open literature, evidence of enhanced susceptibility was demonstrated . . . for methyl parathion via the subcutaneous and intraperitoneal routes."

The methyl parathion exposures in both studies were high dose levels administered directly to rat pups. Thus, this finding should not be included in a summary of prenatal developmental toxicity study results. The discussion in the Hazard Report on page 4 should indicate that there was no evidence for increased susceptibility of the offspring in Guideline developmental toxicity studies of methyl parathion in rats and rabbits (as discussed in the HIARC document, page 19, and in the Safety Factor Report, Attachment 4, page 25). These documents also should be clarified to indicate that the intraperitoneal and subcutaneous exposures referred to in "Literature data" were postnatal exposures only. This point is important for defining the population potentially at risk and also for assessing the relevancy and validity of the assay results for hazard assessment purposes.

The Safety Factor Report states that " . . . evidence of increased susceptibility was seen in prenatal developmental toxicity studies in rats. . . . Although the subcutaneous and intraperitoneal routes of administration are not traditional (i.e., oral), the Committee determined that the demonstration of increased susceptibility, as well as occurrence of neuropathology, warrants the 10X safety factor." As discussed above, the published studies on methyl parathion reflect the results of direct postnatal administration to pups and were not prenatal studies.

Additionally, the methyl parathion studies by the subcutaneous and intraperitoneal routes of administration do not provide relevant data for evaluating comparative susceptibility of pups and adults for the following reasons:

- Single high doses were administered in these studies, which are not relevant to anticipated low-level dietary exposures of infants and small children (residential exposures to methyl parathion are precluded by the labeling of methyl parathion products).

- Administration of high dose volumes of vehicle by either route (but particularly intraperitoneal from injection trauma) may produce increased mortality in neonatal pups. The published intraperitoneal study of methyl parathion included no vehicle control group, so vehicle control mortality could not be evaluated.

As previously noted in comments on the methyl parathion HID document (Attachment B), the report of the March 24-25, 1998, Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Committee, suggested that

> the magnitude and difference of the sensitivity between adults and juveniles should be determined more thoroughly . . . much of this information was generated in acute treatment experiments, frequently at very high exposure levels. Such data may not be appropriate to extrapolate to low-dose situations, e.g., organophosphates, where much, if not all, of the age-related differences may be attributable to differences in the magnitude and activity of detoxification enzymes. *In such cases, differences in toxicity between adults and juveniles would be substantially greater at high doses where detoxification mechanisms are saturated than at low dose levels where they are not* [emphasis added].

Therefore, Cheminova considers that these studies do not provide a basis for finding increased susceptibility to pups, or for retaining the FQPA 10X safety factor.

Attachment D
Residue

Comments on EPA's Residue Chemistry Chapter for the Methyl Parathion Reregistration Eligibility Decision (RED) Document

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38 pages

RESIDUE

This attachment provides comments from Cheminova Agro A/S (Cheminova) on EPA's "Residue Chemistry Chapter for the Methyl Parathion Reregistration Eligibility Decision (RED) Document" (Bonnie Cropp-Kohlligian, June 11, 1998) (EPA Attachment 3), herein referred to as the "Residue Chemistry Chapter."

I. DIRECTIONS FOR USE

The following comment pertains to EPA's section titled *Summary of Science Findings, Directions for Use*. In this section, EPA requests that end-use product labels be amended to specify a minimum spray volume of 2 gal/A for vegetable crops and 10 gal/A for orchard crops. Cheminova notes that it will amend its Methyl Parathion 4EC product label at the conclusion of the RED process to specify a minimum spray volume of 2 gal/A for vegetable crops (but not for cotton, alfalfa, and grass). Cheminova has no supported uses of its emulsifiable concentrate (EC) formulation on orchard crops; Elf Atochem will need to respond to this request. Cheminova is prepared to submit amended labels after the label data call-in (DCI) is issued.

II. NATURE OF THE RESIDUE IN PLANTS

With regard to EPA's statement in the section titled *Nature of the Residue in Plants,* that a new lettuce metabolism study is required, Cheminova notes that it submitted the new lettuce metabolism study to EPA on October 9, 1998 (MRID No. 44669501). Cheminova requests that EPA acknowledge the receipt of the new study in the RED.

Also in the section titled *Nature of the Residue in Plants,* EPA requests that residues of methyl parathion, methyl paraoxon, and paranitrophenol (PNP) be determined in/on plant samples collected from future plant magnitude of the residue studies. Cheminova does not agree with the need to determine residues of PNP in/on crop field trials for reasons stated in Attachment E to Cheminova's response document.

III. NATURE OF THE RESIDUE IN LIVESTOCK

In the section of the Residue Chemistry Chapter titled *Nature of the Residue in Livestock,* EPA requests the submission of additional information and data needed to validate the experimental methods for the poultry and ruminant metabolism studies. Cheminova notes that it submitted the requested information to EPA in a letter dated February 2, 1998 (no MRID number was assigned to this submission). Cheminova requests that EPA acknowledge the receipt of the requested information in the RED.

In the *Nature of the Residue in Livestock* section, EPA also states that the residues of concern in animal commodities are methyl parathion, methyl paraoxon, PNP, and aminoparaoxon-methyl. As explained in more detail in EPA's memorandum titled "The Outcome of the HED Metabolism Assessment Review Committee Meeting Held on March 11, 1998" (herein referred to as the "Metabolism Committee Memorandum"), the Metabolism Committee tentatively decided that the tolerance expression for methyl parathion in animal commodities consists of methyl parathion only, but that methyl parathion residues of concern to be included in the ChE risk assessment for animal commodities include methyl parathion and methyl paraoxon. The committee also tentatively concluded that methyl parathion residues of overall concern in animal commodities are methyl parathion, methyl paraoxon, PNP, and aminoparaoxon-methyl. The Metabolism Committee Memorandum concludes that all four chemical species should be determined in the required livestock feeding studies.

In its April 10, 1997, DCI notice for methyl parathion, EPA requested that milk, eggs, and livestock tissues be analyzed for methyl parathion, methyl paraoxon, and free and conjugated forms of p-aminophenol and PNP. In response to this DCI, Cheminova submitted proposed testing designs for this study on October 27, 1997, in which it proposed to analyze livestock study tissues for methyl parathion and methyl paraoxon only. EPA's new request to include aminoparaoxon-methyl as an analyte and its new calculations of the 1X feeding level in the studies demonstrate that it would have been imprudent to conduct these studies in response to the 1997 DCI.

The Metabolism Committee Memorandum requires analysis of animal products for free PNP, in addition to methyl parathion and methyl paraoxon; however, analysis for aminoparaoxon-methyl is now also required. Cheminova does not believe that animal commodities need to be analyzed for PNP. From a toxicological point of view, PNP does not contain the active phosphorus moiety of methyl parathion and therefore does not inhibit ChE. Available information on the toxicity of PNP indicates that its toxicity is much lower than the ChE-inhibiting toxicity associated with methyl parathion. In addition, PNP lies on the excretory pathway for methyl parathion in animals. Moreover, it is not clear why a registration involving treatment of leather would ever implicate a need for crop residue data for PNP since aggregate risk assessments exclude occupational exposures. Finally, as noted elsewhere in these comments, EPA states in the PNP RED that it has accepted the U.S. Army's voluntary cancellation for the sole remaining use of PNP as an active ingredient. Therefore, there is no need to obtain residue data for PNP in livestock because there is no need for an aggregate risk assessment for PNP as an active ingredient.

With regard to aminoparaoxon-methyl, Cheminova believes that from a residue chemistry point of view EPA's new request to analyze livestock tissues for this metabolite is reasonable, although EPA indicates that its concern is based on neuropathy of unknown origin and not due to ChE inhibition. However, because

aminoparaoxon-methyl is likely to be water soluble, and because there is little or no available analytical experience with this metabolite, Cheminova believes that its analyses in livestock tissues will be difficult. However, Cheminova will attempt to analyze tissues from the cattle and poultry feeding studies for this metabolite.

A further design issue with respect to the livestock feeding studies is the calculation of 1X feeding levels. As discussed in more detail in section V of this attachment, the correct feeding levels need to be calculated before the studies can be conducted.

In the absence of further communication from EPA on the design of the livestock feeding studies, Cheminova thus plans to analyze tissue samples in these studies for methyl parathion, methyl paraoxon, and, if technically possible, aminoparaoxon-methyl. Cheminova plans to conduct these studies in 1999

IV. RESIDUE ANALYTICAL METHODS

In the section titled *Residue Analytical Methods*, EPA requests that an enforcement method be proposed and undergo independent laboratory validation and an Agency method try-out. Cheminova proposes that the FDA multiresidue testing protocols be considered as enforcement method(s) for methyl parathion. Therefore, there is no need for an independent validation or an Agency method try-out.

As stated in the section titled *Residue Analytical Methods*, the RED indicates that all of the residue data on crop and processed commodities were collected using a modification of Elf Atochem Method Number BR-007-00. This method involves extraction with acidic acetone, partitioning with ethyl acetate, cleanup by gel permeation, and determination of methyl parathion and methyl paraoxon by gas liquid chromatography (GLC) using a flame photometric detector operating in the phosphorus mode. Analysis for PNP requires additional cleanup of the extract using a Florisil Sep Pak and analysis by high-performance liquid chromatography (HPLC). Cheminova notes that the above statement is an error. The studies conducted by Cheminova did not use the Elf Atochem analytical method. As stated in the Methyl Parathion Residue Chemistry Reregistration Standard Update (November 20, 1992), the Cheminova study samples were analyzed using a modification of Method I(a) from Pesticide Analytical Manual (PAM), Volume II. This method involves extraction and hydrolysis with methanol:water:HCl mixture, partitioning into ethyl acetate. Residues of methyl parathion and methyl paraoxon are quantified by GLC equipped with a flame photometric detector operated in the phosphorus mode. The ethyl acetate extract is cleaned up using a Florisil column, and residues of PNP are quantified by reverse phase HPLC equipped with an ultraviolet detector.

In the section titled *Multiresidue Method Testing*, EPA states that methyl paraoxon is not recovered by FDA's multiresidue protocol E (fatty and nonfatty). Cheminova

believes that this statement is erroneous. FDA employs a modified multiresidue method in which the Florisil cleanup procedure is eliminated. Using this method, methyl paraoxon is recovered with acceptable results. FDA has been monitoring methyl paraoxon (as well as methyl parathion) for at least six years in a variety of human food items (despite the fact that this compound is not in the tolerance expression). Typically about 300 to 400 samples per year are analyzed in such a fashion that both compounds are detectable (the limit of quantitation is generally 0.01 ppm for both). In 1993, 1994, 1995, 1996, and 1997, no detections of methyl paraoxon were reported by FDA. In 1992 it was detected in two samples of dark sweet cherries (at 0.351 and 0.178 ppm) from Oregon.

V. MAGNITUDE OF THE RESIDUES

In the section titled *Magnitude of the Residue in Crop Plants,* EPA indicated that IR-4 plans to support the use of methyl parathion on hops. Cheminova notes that it has also learned that IR-4 wishes to support the use of methyl parathion on bell peppers and melons. Cheminova is not supporting the use of the EC formulation of methyl parathion on hops, bell peppers, or melons. Cheminova recommends that EPA check with IR-4 concerning the crops it will support.

EPA also stated that pending label amendments, reregistration requirements are fulfilled for a list of 21 crops. Cheminova would like EPA to expand its statement by noting that it also believes that no additional data for the EC formulation are required for potatoes, beans, sugar beet tops, turnip greens, onions, soybeans, Brussels sprouts, cauliflower, collards, lentils, wheat, and all cereal grains.

Also in the section titled *Magnitude of the Residue in Crop Plants,* EPA stated that for the purpose of reregistration, residue data are required for aspirated grain fractions (AGF), alfalfa, almonds, apples, beans, cherries, cottonseed, cotton gin byproducts, grass, onions, peanuts, pears, pecans, plums, potatoes, rice straw, rape forage, sorghum, soybeans, sweet potatoes, sugar beet tops, turnip greens, and wheat. Cheminova notes that it is conducting field trials for alfalfa, grass, cotton, cotton gin byproducts, and wheat (AFG) and anticipates submitting these studies by April 14, 1999. Other than the need for AGF for wheat, Cheminova is not aware of any additional AGF needs. The April 10, 1997, DCI only requested AGF data for wheat, and Cheminova is generating these data. Cheminova requests that EPA clarify the need for AGF data other than for wheat.

Cheminova is not conducting studies on almonds, apples, cherries, hops, peanuts, pears, pecans, plums, sorghum, sweet potatoes, and rape forage because it is not supporting uses on these crops for the EC formulation. Based on the 1997 DCI, Cheminova is not aware of any data gaps for the EC formulation for any of the Cheminova-supported crops except as noted above. Cheminova believes that

sufficient data are available for representative cereal grains to support a cereal grain crop group tolerance; therefore, Cheminova does not agree that residue data are required for rice straw. Cheminova requests that EPA clarify whether or not it believes that sufficient data are available to support a cereal grain crop group tolerance.

Label amendments will be submitted in response to a generic label DCI to be issued as part of the RED to resolve any outstanding issues for all supported crops including beans, potatoes, onions, soybeans, sugar beets, turnips, and wheat. EPA should clarify the need for any additional residue data using the EC formulation for AGF (except wheat), beans, onions, potatoes, rice, soybeans, sugar beets, turnips, and wheat.

On page 9 of the Residue Chemistry Chapter, EPA states that residue data are required for sweet potato. In Table B (page 36) of the same document, EPA contradicts itself by stating that it will translate potato residue data to support sweet potato. Cheminova notes that is not supporting the use of the EC formulation on sweet potatoes; therefore, no data are required for this formulation. Elf Atochem, however, will support the use of the Mcap formulation on sweet potatoes and intends to translate data from white potatoes to support this use.

In the section titled *Magnitude of the Residue in Processed Food/Feed*, EPA states that processing studies are required for peanuts, plums/prunes, and sunflower seeds. Cheminova is conducting the sunflower processing study and will submit it by April 14, 1999. Because Cheminova is not supporting the use of the EC formulation of methyl parathion on peanuts and plums, it is not conducting any processing studies for these crops. Elf Atochem is supporting the use of the Mcap formulation on plums and peanuts; it has or will soon submit the necessary processing data to support the use of the Mcap formulation on these crops.

In the section titled *Magnitude of the Residue in Meat, Milk, Poultry, and Eggs,* EPA stated that magnitude of the residue data on meat, milk, poultry, and eggs are required. In the April 10, 1997 DCI, EPA calculated 1X feeding levels of 3 ppm for cattle and 1 ppm for poultry. However, in the draft RED, EPA recalculated the 1X dose levels to be 32 ppm for cattle and 5 ppm for poultry. These new feeding level calculations are incorrect for two reasons. First, they are based on EPA's opinion on what the revised tolerance levels for corn forage and stover should be, based on a zero-day pre-harvest interval (PHI)for sweet corn treated with Penncap-M®. Elf Atochem is not supporting the zero-day PHI for Penncap-M®. Secondly, in order to calculate the correct 1X dose levels for the feeding studies, the results of the alfalfa, cotton and grass field trials currently being conducted must be considered. These studies are scheduled to be submitted in April 1999. Cheminova thus plans to conduct the livestock feeding studies in 1999. (See Section III above concerning the analytes to be measured in animal products in these studies.)

In the section titled *Confined Accumulation in Rotational Crops,* EPA stated that the required confined rotational crop data (MRID 43127609) are under review. Cheminova notes that it submitted these data to EPA on February 15, 1994. Cheminova requests that the Agency complete its review of these data and use these data in completing the RED.

VI. COMMENTS ON EPA'S TABLES IN THE RESIDUE CHEMISTRY CHAPTER

EPA's Table A in the Residue Chemistry Chapter is titled "Food/Feed Use Patterns Subject to Reregistration for Methyl Parathion." In the main document to this attachment, Cheminova provides clarification of the food/feed uses and use patterns that Cheminova will support for reregistration (Tables 1-6).

EPA's Table B in the Residue Chemistry Chapter, titled "Residue Chemistry Science Assessments for Reregistration of Methyl Parathion", provides the Agency's evaluation of the adequacy of the residue chemistry database for methyl parathion. Table D-1, in the appendix to this attachment, provides Cheminova's response to the Agency's evaluation of the adequacy of the database for the EC formulation. Table D-2 of the appendix to this attachment provides Elf Atochem's response to the information presented in EPA's Table B with respect to Mcap formulation.

Cheminova's and Elf Atochem's comments on EPA's Table C in the Residue Chemistry Chapter, titled "Tolerance Reassessment Summary for Methyl Parathion", are provided in Table D-3, in the appendix to this attachment.

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APPENDIX to Attachment D
Residue Chemistry

Table D-1. Residue Chemistry Data Requirements for the Emulsifiable Concentrate Formulation and Cheminova's Response

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
860.1200: Directions for Use	The registrant must amend all end-use product labels to specify a minimum spray volume of 2 gallons per acre for vegetable crops and 10 gallons per acre for orchard crops unless they specifically wish to support ULV applications of methyl parathion to crops (other than cotton).	In response to a generic end-use label data call-in issued with the RED, Cheminova will amend its end-use labels to specify a minimum spray volume of 2 gallons per acre for all crops except alfalfa, cotton, and grass.
860.1300: Plant Metabolism	A new lettuce metabolism study is required.	Cheminova submitted the repeat lettuce metabolism study to EPA on October 9, 1998 (MRID 44669501).
860.1300: Animal Metabolism	The following additional data are required to validate the experimental methods for the poultry and ruminant metabolism studies: (1) the in-life portion of the study, including total feeds consumed to determine theoretical dietary intake of methyl parathion, as ppm, in the feed; (2) the storage intervals for goat tissue, milk, hen tissue, and egg samples; and (3) for the ruminant study only, the specific fraction or matrix used for Soxhlet extraction, acid hydrolysis, and enzyme hydrolysis.	Cheminova submitted the requested information to EPA in a letter dated February 2, 1998 (no MRID was assigned to this submission).

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
860.1360: Residue Analytical Methods:		
- Plant commodities	The proposed enforcement method employed to determine methyl parathion and methyl paraoxon in plant commodities must undergo an independent laboratory validation at which time the Agency will perform a method trial on the procedure. If additional metabolites of concern are identified in the outstanding lettuce metabolism study, additional analytical methods may be required.	Cheminova requests that the FDA multiresidue method be used as the enforcement method. According to EPA guidance, no ILV is required if an FDA multiresidue method is used as the enforcement method.
- Animal commodities	In conjunction with the ruminant and poultry feeding studies, the registrants must provide data validating the analytical method(s) used for determining methyl parathion, methyl paraoxon, *p*-nitrophenol, and amino-paraoxon-methyl in meat, milk, poultry, and eggs. If the feeding studies indicate that tolerances are necessary for residues in animal commodities, then the registrants must propose an enforcement method for determining residues of methyl parathion in animal commodities.	In its 7/14/97 response to the 4/10/97 DCI, Cheminova states that it will conduct an independent laboratory validation of a method detecting parent and oxon in animal tissues after the animal feeding studies are submitted. Cheminova told EPA that it would not initiate the animal feeding studies until EPA responds to Cheminova's draft testing proposals that were submitted to EPA on October 27, 1997. EPA has not formally responded to the draft testing proposals. The ILV will be conducted after the methods are developed for the animal feeding studies. Regarding the recent conclusions from EPA's metabolism committee decision that these studies must include analysis for p-nitrophenol and amino-paraoxon-methyl, Cheminova believes there is no reason to analyze for p-nitrophenol but will attempt to analyze for amino-paraoxon-methyl. In the absence of further communication from EPA on the design of the livestock feeding studies, Cheminova thus plans to analyze samples in these studies for methyl parathion, methyl paraoxon, and, if possible, amino-paraoxon-methyl.
860.1360: Multiresidue Methods	No additional data are required.	No action required.
860.1380: Storage Stability Data-Plant Commodities	Data depicting the storage stability of methyl parathion residues of concern in/on a representative fruit are required.	Cheminova is not supporting the use of the EC formulation on any member of the fruiting vegetable crop group. See Table D-2 for Elf Atochem's response to this requirement.
860.1380: Storage Stability Data-Animal Commodities	Data depicting the storage stability of methyl parathion residues of concern in animal commodities are required in conjunction with the ruminant and poultry feeding studies.	Cheminova will include the required storage stability data for meat, eggs, and milk when it submits the animal feeding studies.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
860.1500: Magnitude of the Residue Crop Field Trials		
Root and Tuber Vegetables		
- Beets, garden, roots	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova is not supporting the use of the EC formulation on this crop and will not object if EPA revokes this tolerance.
- Carrots	No additional data are required provided label amendments are submitted in response to the RED specifying the maximum seasonal use.	Cheminova agrees to amend its labels as part of a generic label data call-in notice issued with the RED.
- Parsnips	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova is not supporting the use of the EC formulation on this crop and will not object if EPA revokes this tolerance.
- Potatoes	The available data are adequate to support the use of the EC formulation of methyl parathion on potatoes and indicate that the currently established tolerance for residues of methyl parathion in/on potatoes should be lowered from 0.1 ppm to 0.05 pm (MRID 41438102). No data are available to support the use of the Mcap formulation on potatoes.	In the 4/10/97 DCI, EPA states that these data (MRID 41438102) are acceptable for supporting the use of the EC formulation on potatoes provided label amendments are submitted specifying the maximum seasonal use. Cheminova agrees to amend its labels as part of a generic label data call-in notice issued with the RED. See Table D-2 for Elf Atochem's response. Cheminova believes EPA should assess this tolerance after Elf Atochem submits the data needed to support the use of the Mcap formulation on potatoes.
- Radishes	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova is not supporting the use of the EC formulation on this crop and will not object if EPA revokes this tolerance.
- Rutabagas	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and that the tolerance for this crop should be revoked.
- Sugar beet roots	The available data are adequate (MRID 41379306) pending submission of label amendments specifying the maximum seasonal use patterns supported by the submitted residue data. Available data support lowering the tolerance from 0.1 ppm to 0.05 ppm.	Cheminova agrees to submit the required label amendments as part of a generic label data call-in issued with the RED.
- Sweet potatoes and yams	Available potato field trial data generated with an EC formulation indicate that the tolerance in/on sweet potatoes should be lowered from 0.1 ppm to 0.05 ppm.	Cheminova is not supporting the use of EC formulation of methyl parathion on this crop; however, Elf Atochem holds a 24 (c) registration of the Mcap formulation on this crop. See Table D-2 for Elf Atochem's response.
- Turnip roots	The submitted data are adequate to support the use of the EC formulation on turnip roots provided label amendments are submitted specifying the maximum seasonal use and increasing the PHI to 15 days. The available data (MRID 41717806) are adequate and support lowering the tolerance from 1 ppm to 0.05 ppm.	Cheminova agrees to submit the required label amendments as part of a generic label data call-in issued with the RED.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
Leaves of Root and Tuber Vegetables		
- Beets garden green	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object if EPA revokes this tolerance.
- Parsnip greens	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object if EPA revokes this tolerance.
- Radish tops	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object if EPA revokes this tolerance.
- Rutabaga tops	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object if EPA revokes this tolerance.
- Sugar beet tops	Data are acceptable (MRID 41379306) provided label amendments are submitted. The available data support establishing a 60-day PHI on sugar beet tops; however, a 60 day PHI is not practically enforceable for sugar beet tops since a 20-day PHI is established on sugar beet roots. Based on the translation of turnip green tops data (MRID 41717806) to sugar beet tops, the currently established tolerance for residues of methyl parathion in/on sugar beet tops should be increased from 0.1 ppm to 2 ppm.	Cheminova agrees to submit label amendments as required in response to a generic label data call-in notice issued with the RED.
- Turnip greens	The submitted data (MRID 41395101) are acceptable to support the use of the EC formulation on turnip greens provided that label amendments are submitted specifying the maximum seasonal use and increasing the PHI to 15 days. Data are acceptable (MRID 41717806) and support establishing a 21-day PHI; however, a 21 day PHI is not practically enforceable since a 15-day PHI is established on sugar beet roots. Based on these data, the currently established tolerance in/on turnip greens should be increased from 1 ppm to 4 ppm.	Cheminova agrees to submit label amendments specifying the maximum seasonal use in response to a generic label data call-in notice issued with the RED.
Bulb Vegetables		
- Garlic	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object if EPA revokes this tolerance.

- Onions	The available data (MRIDs 41395104 and 41596203) are adequate to support the use of the EC formulation on onions and indicate that the currently established tolerance for residues in/on onions (1 ppm) is appropriate. Data are adequate to support the use of the EC formulation on this crop provided label amendments are submitted specifying the maximum seasonal use.	Cheminova agrees to submit label amendments specifying the maximum seasonal use in response to a generic label data call-in notice issued with the RED.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
Leafy Vegetables (except Brassica)		
- Celery	The available data (MRID 41717802) are adequate and indicate that the currently established tolerance in/on celery should be increased from 1 ppm to 5 ppm. Data are adequate to support the use of the EC formulation on this crop provided label amendments are submitted specifying the maximum seasonal use.	Cheminova agrees to submit label amendments specifying the maximum seasonal use in response to a generic label data call-in notice issued with the RED.
- Endive	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object if EPA revokes this tolerance.
- Lettuce	The available data (MRIDs 41379302 and 41596204) are adequate and indicate that the currently established tolerance in/on lettuce should be increased from 1 ppm to 2 ppm. Data are adequate to support the use of the EC formulation on this crop provided label amendments are submitted specifying the maximum single and seasonal use rates and PHIs supported by submitted residue data.	Cheminova agrees to submit label amendments specifying the maximum seasonal use in response to a generic label data call-in notice issued with the RED.
- Parsley	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object if EPA revokes this tolerance.
- Spinach	The available data (MRID 41359906) are adequate and indicate that the currently established tolerance in/on spinach should be lowered from 1 ppm to 0.5 ppm. Adequate data have been submitted to support the use of the EC formulation on this crop provided label amendments are submitted specifying the maximum single and seasonal use rates and PHIs supported by submitted residue data	Cheminova agrees to submit label amendments specifying the maximum seasonal use in response to a generic label data call-in notice issued with the RED.
- Swiss Chard	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object if EPA revokes this tolerance.
Brassica Leafy Vegetables		
- Broccoli	Adequate residue data have been submitted to support the EC formulation on this crop provided label amendments are submitted specifying the maximum seasonal use. Adequate broccoli, cabbage, and mustard green data are available and support a 1.0 ppm tolerance in/on *Brassica* vegetables crop group. Individual tolerances should be revoked.	Cheminova agrees to submit label amendments specifying the maximum seasonal use in response to a generic label data call-in notice issued with the RED. In addition, Cheminova will not object to the establishment of a *Brassica* vegetables crop group tolerance.
- Brussels Sprouts	Adequate broccoli, cabbage, and mustard green data are available and support the 1.0 ppm tolerance in/on *Brassica* vegetables crop group. Individual tolerances should be revoked.	Cheminova will not object to the establishment of a *Brassica* vegetables crop group tolerance.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
- Cabbage	Adequate residue data have been submitted to support the EC formulation on this crop provided label amendments are submitted specifying the maximum seasonal use. In addition, adequate broccoli, cabbage, and mustard green data are available and support the 1.0 ppm tolerance in/on *Brassica* vegetables crop group. Individual tolerances should be revoked.	Cheminova agrees to submit label amendments specifying the maximum seasonal use in response to a generic label data call-in notice issued with the RED. In addition, Cheminova will not object to the establishment of a *Brassica* vegetables crop group tolerance.
- Cauliflower	Adequate broccoli, cabbage, and mustard green data are available and support the 1.0 ppm tolerance in/on *Brassica* vegetables crop group. Individual tolerances should be revoked.	Cheminova will not object to the establishment of a *Brassica* vegetables crop group tolerance.
- Collards	Adequate broccoli, cabbage, and mustard green data are available and support the 1.0 ppm tolerance in/on *Brassica* vegetables crop group. Individual tolerances should be revoked.	Cheminova will not object to the establishment of a *Brassica* vegetables crop group tolerance.
- Kale	Adequate broccoli, cabbage, and mustard green data are available and support the 1.0 ppm tolerance in/on *Brassica* vegetables crop group. Individual tolerances should be revoked.	Cheminova will not object to the establishment of a *Brassica* vegetables crop group tolerance.
- Kohlrabi	Adequate broccoli, cabbage, and mustard green data are available and support the 1.0 ppm tolerance in/on *Brassica* vegetables crop group. Individual tolerances should be revoked.	Cheminova will not object to the establishment of a *Brassica* vegetables crop group tolerance.
- Mustard Greens	Adequate residue data have been submitted to support the EC formulation on this crop provided label amendments are submitted specifying the maximum seasonal use. In addition, adequate broccoli, cabbage, and mustard green data are available and support the 1.0 ppm tolerance in/on *Brassica* vegetables crop group. Individual tolerances should be revoked.	Cheminova agrees to submit label amendments specifying the maximum seasonal use in response to a generic label data call-in notice issued with the RED. In addition, Cheminova will not object to the establishment of a *Brassica* vegetables crop group tolerance.
Legume Vegetables		
- Beans, succulent and dried	Adequate data have been submitted to support the use of the EC formulation on dried and succulent beans provided label amendments are submitted specifying the maximum season use. Additional data are required for the use of the Mcap formulation on dried and succulent beans. In addition, separate tolerances for dried and succulent beans must be established.	Cheminova agrees to submit label amendments specifying the maximum seasonal use in response to a generic label data call-in notice issued with the RED. In addition, Cheminova requests that the Agency assess the tolerances for dried and succulent beans after Elf Atochem submits the required data to support the use of the Mcap formulation on these crops.
- Guar beans	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
- Peas succulent and dried	Adequate data have been submitted to support the use of the EC formulation on dried and succulent peas provided label amendments are submitted to reflect maximum single and seasonal use rates and the PHIs supported by the submitted residue data. The available pea field trial data (succulent and dried) (MRIDs 41596207 and 42241601) are adequate and support the establishment of separate tolerances for residues of methyl parathion in/on dried pea seeds at 0.5 ppm and in/on succulent peas at 1 ppm.	Cheminova agrees to submit label amendments specifying the maximum seasonal use in response to a generic label data call-in notice issued with the RED.
- Soybeans	Data are required depicting methyl parathion residues of concern in/on soybeans harvested 14 days following the last of 2 applications of the EC formulation at 1 lb a.i./A/application. If quantifiable residues are found on soybeans, then AGF data will also be required. Alternatively, Cheminova can amend the EC product label to specify a maximum use rate of 2 applications/season at 0.5 lb a.i./A/application with a 14-day PHI; this use pattern is supported by the available residue data. Data are also required to support the use of the Mcap formulation on this crop.	In its 7/14/98 response to the DCI, Cheminova agreed to amend its labels as specified in the DCI rather than conduct new field trials. Cheminova agrees to submit an amendment for its EC formulation label specifying a maximum use rate of 2 applications per season at 0.5 lb a.i. per acre per application with a 14-day PHI in response to a generic label data call-in notice issued with the RED. See Table D-2 for Elf Atochem's response to the requirement for data on the Mcap formulation.
Foliage of Legume Vegetables		
- Beans forage and hay	Bean vines and hay are no longer listed as RACs of beans. The only bean species having foliage RACs is cowpea, for which forage and hay are RACs. The available data on bean vines and hay (MRID 41517102), submitted to support the use of the EC formulation on beans, would be adequate to support a tolerance of 4 ppm for residues of methyl parathion in/on cowpea hay harvested 15 days following the last of six applications of the EC formulation at 1.5 lb a.i./A/application. However, no data are available for cowpea forage. The registrants must either (1) amend the use pattern for beans to exclude applications to cowpeas or (2) provide adequate residue data for cowpea forage reflecting the maximum use rate of the EC formulation to peas and propose tolerances for residues in/on cowpea forage and hay.	Cheminova will amend its EC labels to exclude applications of methyl parathion to cowpeas in response to a generic label data call-in notice issued with the RED. See Table D-2 for Elf Atochem's response for the Mcap formulation.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
- Pea vines and hay	Pea vines and hay are no longer listed as RACs of pea. Only vines and hay of field pea cultivars grown as livestock feeds are listed as RACs. The available data on pea vines and hay (MRIDs 41596207 and 42241601) would be adequate to support tolerances for residues of methyl parathion in/on field pea vines and hay harvested 15 days following the last of six applications of an EC formulation at 1 lb a.i./A/application; these data would support tolerances of 60 and 15 ppm for residues in/on field pea vines and hay. The registrants must either (1) amend the use pattern for peas to exclude applications to field peas grown for livestock feed or (2) propose tolerances for field pea vines and hay.	Cheminova agrees to submit label amendments to exclude applications to field peas grown for livestock feed in response to a generic label data call-in notice issued with the RED. See Table D-2 for Elf Atochem's response for the Mcap formulation.
- Soybeans forage and hay	Data are required depicting residues of concern in/on soybean forage and hay reflecting the maximum use rates on soybeans for the EC (and Mcap) formulations. Alternatively, if the product labels are amended to prohibit the feeding of treated soybean forage and hay to livestock, then residue data on soybean forage and hay will not be required and associated tolerances should be revoked.	Cheminova agrees to submit label amendments prohibiting the feeding and grazing of forage and hay in response to a generic label data call-in notice issued with the RED. See Table D-2 for Elf Atochem's response for the Mcap formulation.
Fruiting Vegetables		
- Eggplant	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object if EPA revokes this tolerance.
- Peppers	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova is not supporting the use of methyl parathion on this crop; however, it understands that IR-4 may be supporting this use.
Cucurbit Vegetables		
- Cucumbers	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object if EPA revokes this tolerance.
- Melons	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova is not supporting the use of methyl parathion on this crop; however, it understands that IR-4 may be supporting this use.
- Pumpkins	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object if EPA revokes this tolerance.
- Squash	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object if EPA revokes this tolerance.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
Citrus Fruits		
- Citrus	No data are required; the use of methyl parathion on citrus fruits is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object if EPA revokes this tolerance.
Pome Fruits		
- Quince	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object if EPA revokes this tolerance.
Stone Fruits Group		
- Apricots	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object if EPA revokes this tolerance.
Berries Group		
- Blackberries	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that these crops are not being supported and will not object if EPA revokes these tolerances.
- Blueberries (huckleberries)	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	
- Boysenberries	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	
- Currants	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	
- Dewberries	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	

- Gooseberries	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	
- Loganberries	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
- Raspberries	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that these crops are not being supported and will not object if EPA revokes these tolerances.
- Youngberries	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	
Tree Nuts Group		
- Filberts	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object if EPA revokes this tolerance.
Cereal Grains		
- Aspirated Grain Fractions - Field Corn	Data are required depicting methyl parathion residues of concern in aspirated grain fractions derived from field corn harvested at the appropriate PHIs following treatment at the maximum labeled rates.	This requirement for AGF data in field corn was not required in the 4/10/97 DCI. However, EPA now states these AGF data are required. Cheminova requests that EPA clarify the need for AGF data for field corn. See Table D-2 for comments from Elf Atochem for the Mcap formulation.
- Aspirated Grain Fractions - Grain Sorghum	Data are required depicting methyl parathion residues of concern in aspirated grain fractions derived from grain sorghum harvested at the appropriate PHIs following treatment at the maximum labeled rates.	Cheminova is not supporting the use of methyl parathion on sorghum, thus data on residues in AGF derived from grain sorghum are not required.
- Aspirated Grain Fractions - Soybeans	Data are required depicting methyl parathion residues of concern in aspirated grain fractions derived from soybeans harvested at the appropriate PHIs following treatment at the maximum labeled rates.	In the 4/10/97 DCI, EPA stated that AGF data would be required for soybeans if the field trials show quantifiable residues on the soybeans. Because Cheminova chose to reduce its maximum labeled rate to the rate tested in the submitted field trials (soybeans harvested 14-15 days after the last of two applications at 0.5 lb a.i./A), and because residue from those trials were nondetectable, no AGF data should be required. Cheminova does not agree AGF data are required for the EC formulation on soybeans. See Table D-2 for a response from Elf Atochem for the Mcap formulation.
- Aspirated Grain Fractions - Wheat	Data are required depicting methyl parathion residues of concern in aspirated grain fractions derived from wheat grain harvested at the appropriate PHIs following treatment at the maximum labeled rates.	In its response to the 4/10/97 DCI, Cheminova stated that it would provide the Agency with residue data for wheat AGF. The wheat AGF study is ongoing.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
- Barley	No data are required. Residue data on wheat grain, forage, hay, and straw will be translated to support uses on barley (grain, hay, and straw), oats (grain, forage, hay, and straw), and rye (grain, forage and straw).	Cheminova agrees that wheat data shall be translated to support the use of methyl parathion on barley. Cheminova believes that sufficient data are available for representative cereal grains to support a cereal grain crop group tolerance. Cheminova will not object to EPA establishing a cereal grain crop group tolerance.
- Corn	The available data are adequate and support the establishment of separate tolerances for residues of methyl parathion in/on sweet corn (K+CWHR), field corn grain, and pop corn grain at 0.2 ppm. The registrant should amend all labels to specify the minimum PHIs and maximum single and seasonal use rates supported by the available data. Available sweet corn field trial data support a PHI of 3 days following the last of six foliar applications at 1 lb a.i./A/application. Available field corn field trial data support a PHI of 12 days following the last of six foliar applications at 1 lb a.i./A/application.	In its 7/14/98 response to the 4/10/97 DCI, Cheminova agreed to amend its labels to reflect maximum single and seasonal use rates and PHIs supported by submitted residue data. These label amendments will be submitted in response to a generic label data call in issues with the RED. Cheminova believes that sufficient data are available for representative cereal grains to support a cereal grain crop group tolerance. Cheminova will not object to EPA establishing a cereal grain crop group tolerance.
- Oats	No data are required. Residue data on wheat grain will be translated to support uses on oat grain.	Cheminova agrees with EPA's position that wheat data shall be translated to support the use on oats. Cheminova believes that sufficient data are available for representative cereal grains to support a cereal grain crop group tolerance. Cheminova will not object to EPA establishing a cereal grain crop group tolerance.
- Rice	Available data are adequate and indicate that the currently established tolerance in/on rice should be increased from 1 ppm to 3 ppm.	The 4/10/97 DCI required Cheminova to amend its labels to specify the maximum single and seasonal use rates and PHIs supported by submitted residue data and to specify that applications to rice are to be made using aerial equipment only. In its 90-day response to the DCI, Cheminova agreed to amend its labels as required in response to a generic label data call-in notice issued with the RED. Cheminova believes that sufficient data are available for representative cereal grains to support a cereal grain crop group tolerance. Cheminova will not object to EPA establishing a cereal grain crop group tolerance.
- Rye	No data are required. Residue data on wheat grain, forage, hay, and straw will be translated to support uses on barley (grain, hay, and straw), oats (grain, forage, hay, and straw), and rye (grain, forage and straw).	Cheminova agrees that wheat data shall be translated to support the use of methyl parathion on rye. Cheminova believes that sufficient data are available for representative cereal grains to support a cereal grain crop group tolerance. Cheminova will not object to EPA establishing a cereal grain crop group tolerance.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
- Sorghum	Additional residue data are required on sorghum grain, forage, and stover because the available data do not reflect the registered use pattern. The registered use specifies a maximum seasonal rate of 6 applications at up to 0.20 lb a.i./A/application with an EC formulation of methyl parathion and a 21-day PHI/PGI. The available residue data reflect 6 applications at 1 lb a.i./A/application with a 21-day PHI (5x the use rate) and indicate that residues would exceed the established tolerances on sorghum grain and forage at that rate. New sorghum field trials are required to support the currently registered maximum use rate of the EC formulation of methyl parathion on sorghum and should include residue data on grain, forage, and stover. Data are also required for residues in/on sweet sorghum unless the registrant amends labels to prohibit the use on sweet sorghum.	Cheminova is not interested in supporting the use of methyl parathion on sorghum and will amend its product labels to remove sorghum in response to a generic label data call-in issues with the RED. Cheminova believes that sufficient data are available for representative cereal grains to support a cereal grain crop group tolerance. Cheminova will not object to EPA establishing a cereal grain crop group tolerance, except sorghum.
- Wheat	The available data are not adequate to support the use of the EC formulation of methyl parathion on wheat. Additional data are required reflecting the currently registered maximum use rate of the EC formulation of methyl parathion on wheat grain. Available wheat field trial data (reflecting use rates which are slightly higher than the currently registered maximum use rate of the EC formulation of methyl parathion on wheat) indicate that the currently established tolerance for residues of methyl parathion in/on wheat grain should be increased from 1 ppm to 4 ppm.	***Wheat Grain:*** Above tolerance residues were reported in the submitted field trials on wheat grain. The 4/10/97 DCI gave Cheminova the option of petitioning for a higher tolerance or submitting new field trials conducted at a lower application rate or a PHI higher than the current PHI of 14 days. In Cheminova's 90-day response to the DCI, Cheminova stated that it is interested in obtaining a cereal grain crop group tolerance and that it believes sufficient residue data are available to support a crop group tolerance. Therefore, Cheminova believes that no additional residue data for wheat grain are needed at this time. ***Wheat AGF:*** The 4/10/97 DCI required that Cheminova submit residue data for wheat AGF. In its 90-day response to the DCI, Cheminova agreed that it would provide the Agency with residue data for wheat AGF. The wheat AGF field trial is ongoing. ***Label amendments*** The 4/10/97 DCI required Cheminova to submit label amendments to specify the maximum seasonal use pattern that are supported by available residue data. In its 90-day response to the DCI, Cheminova agreed to amend its labels as required. Cheminova requests that these label amendments be handled in response to a generic label DCI issued with the RED.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
Forage Fodder and Straw of Cereal Grains		
- Barley hay and straw	Residue data on wheat grain, forage, hay, and straw will be translated to support uses on barley (grain, hay, and straw), oats (grain, forage, hay, and straw), and rye (grain, forage and straw). Available wheat field trial data indicate that tolerances for residues of methyl parathion in/on wheat forage, hay, and straw should be established at 2 ppm, 3 ppm, and 6 ppm, respectively. Since wheat forage, hay, and straw data are being translated to barley hay and straw, tolerances for barley hay and straw should be established at 3 ppm and 6 ppm, respectively.	Cheminova agrees that the submitted wheat data can be translated to support the use of methyl parathion on barley.
- Corn forage and stover	The available data are adequate and indicate that the currently established tolerance for residues of methyl parathion in/on corn forage should be increased from 1 ppm to 20 ppm based on the highest residue level found in forage.	Cheminova agrees that the submitted data are adequate to support this use. See Table D-2 for Elf Atochem's response for the Mcap formulation.
- Oat forage, hay and straw	Residue data on wheat forage, hay, and straw will be translated to support uses on oats (forage, hay, and straw). Available wheat field trial data indicate that tolerances for residues of methyl parathion in/on wheat forage, hay, and straw should be established at 2 ppm, 3 ppm, and 6 ppm, respectively. Since wheat forage, hay, and straw data are being translated to oat forage, hay and straw, tolerances for oat hay and straw should be established at 2 ppm, 3 ppm, and 6 ppm, respectively.	Cheminova agrees that the submitted wheat data can be translated to support the use of methyl parathion on oats.
- Rice straw	The available rice straw data are adequate to support the use of the EC formulation of methyl parathion on rice and indicate that a 9 ppm tolerance for residues of methyl parathion in/on rice straw should be established.	Cheminova agrees that the submitted data are adequate to support this use.
- Rye forage and straw	Residue data on wheat forage and straw will be translated to support the use of methyl parathion on rye forage and straw. Available wheat field trial data indicate that tolerances for residues of methyl parathion in/on wheat forage, hay, and straw should be established at 2 ppm, 3 ppm, and 6 ppm, respectively. Since wheat forage, hay, and straw data are being translated to rye forage and straw, tolerances for rye forage and straw should be established at 2 ppm and 6 ppm, respectively.	Cheminova agrees that submitted wheat data can be translated to support the use of methyl parathion on rye.

- Sorghum forage and stover	Additional residue data are required on sorghum grain, forage, and stover because the available data do not reflect the registered use pattern.	Cheminova will no longer support the use of methyl parathion on sorghum. Cheminova will amend its product labels to remove sorghum.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
- Wheat forage, hay and straw	The available data are not adequate to support the use of the EC formulation of methyl parathion on wheat. In conjunction with the requirement for new field trials for wheat grain to support use of the EC formulations of methyl parathion on wheat, new field trial data are required on wheat forage, hay, and straw reflecting the maximum use rate on wheat. Available wheat field trial data indicate that tolerances for residues of methyl parathion in/on wheat forage, hay, and straw should be established at 2 ppm, 3 ppm, and 6 ppm, respectively.	The requirement for new data for wheat forage, hay, and straw is contingent on the requirement for new data on wheat grain. Cheminova believes that no additional data are needed for wheat grain (see comments for wheat in the cereal grains section of this table); therefore, no additional data are needed for wheat forage, hay and straw.
Grass Forage Fodder and Hay		
- Grass forage and hay	Data are required depicting methyl parathion residues of concern in/on grass forage (at a 0-day PHI/PGI) and hay reflecting the maximum use rate of the EC formulation of methyl parathion on grass.	In its 90-day response to the 4/10/97 DCI, Cheminova agreed to provide EPA with data from field trials with the EC formulation on grasses harvested on day zero after application. At that time, Cheminova informed EPA that that Cheminova would provide these data by April 14, 1999. These field trials are ongoing.
Non-Grass Animal Feeds		
- Alfalfa (fresh) and alfalfa hay	New alfalfa field trials are required depicting residues of concern in/on alfalfa seed, forage, and hay.	An alfalfa study is ongoing, which will provide residue data on alfalfa forage and hay. In its 90-day response to the 4/10/97 DCI, Cheminova stated that it is not supporting the use of the EC formulation on alfalfa grown for seed. Cheminova will amend its end-use labels to prohibit use of the EC formulation on alfalfa grown for seed in response to a generic label data call in issues with the RED.
- Clover	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Trefoil forage	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Trefoil hay	No data are required; the use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Vetch forage and hay	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
Miscellaneous Commodities		
- Artichokes	Provided that Cheminova amends its EC product label to specify a maximum use rate to artichokes of 4 applications/season at 1 lb a.i./A/application with a 7-day PHI, available residue data (MRID 41717801) are adequate and indicate that the currently established tolerance on artichokes should be increased from 1 ppm to 2 ppm. EPA noted that artichokes are not currently listed on Cheminova's EC product label.	Cheminova agrees to amend its labels in response to a generic data call-in notice issued with the RED. Note: According to Cheminova's records, the study submitted on artichokes (globe) is MRID 41379301, not MRID 41717801.
- Avocados	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Cottonseed	Residue data for the EC formulation on cottonseed indicate that the established tolerance will be exceeded based upon the present use pattern. Available data indicate the currently established tolerance in/on cottonseed should be increased from 0.75 ppm to 5 ppm. The registrant must amend the product labels to specify a maximum seasonal use rate supported by the available data.	Cheminova agrees to amend its labels in response to a generic data call-in notice issued with the RED.
- Cotton, gin byproducts	Residue data on cotton gin byproducts are required.	In its 90-day response to the 4/10/97 DCI, Cheminova agreed to provide the Agency with residue data for cotton gin by-products. Cheminova informed EPA that Cheminova would provide these data by April 14, 1999. This study is in progress.
- Cranberries	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Dates	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Figs	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Guavas	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Hops	Although not supported by the basic producers, IR-4 plans to support the use of methyl parathion on hops. Field trial data depicting methyl parathion residues of concern in/on mature dried hops reflecting the proposed maximum use rate of methyl parathion on hops are required.	Cheminova is not supporting the use of methyl parathion on this crop; however, it understands that IR-4 may support this use.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
- Mangoes	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Mustard Seed	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Okra	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Olives	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Pineapples	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Rape seed	The available data are adequate for rape/canola seed and support the established 0.2 ppm tolerance provided the registrants amend product labels to specify a maximum of two applications per season a 0.5 lb a.i./A/application. However, data are required depicting residues in/on rape forage harvested following two applications of methyl parathion EC at 0.5 lb a.i./A/application. Alternatively, the registrant can amend product labels to specify applications only to canola, in which case, data on forage will not be required.	Cheminova will amend its labels to specify that methyl parathion can be made to canola only in response to a generic label data call in issued with the RED.
- Safflower seed	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Strawberries	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Sugarcane	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Sunflower seed	The submitted data (MRID 41359904) are adequate to support the use of methyl parathion on sunflowers.	Cheminova agrees.
- Tobacco	No data are required; use of methyl parathion on this crop is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
860.1520 Processed Food/Feed		
- Barley	No data are required. Processing data from wheat grain will be translated to determine the need for tolerances in processed commodities of barley grain, oat grain, and rye grain.	Cheminova agrees.
- Citrus	No data are required; use of methyl parathion on this commodity is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Corn (field)	No data are required. The data already submitted by Cheminova are sufficient (MRID 41717804).	Cheminova agrees.
- Cottonseed	No data are required. The data already submitted by Cheminova are sufficient (MRID 41597903).	Cheminova agrees.
- Figs	No data are required; use of methyl parathion on this commodity is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Grapes	No data are required. The already submitted data are sufficient (MRID 41597903).	Cheminova is not supporting the EC formulation for use of methyl parathion on grapes. See Table D-2 for Elf Atochem's response for the Mcap formulation.
- Oats	No data are required. Processing data from wheat grain will be translated to determine the need for tolerances in processed commodities of oat grain.	Cheminova agrees.
- Olives	No data are required; use of methyl parathion on this commodity is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Pineapple	No data are required; use of methyl parathion on this commodity is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Potato	No data are required. The data already submitted by Cheminova is sufficient (MRID 41438102).	Cheminova agrees.

- Rapeseed	The available data (MRID 42717602) are adequate for rape/canola seed and support the established 0.2 ppm tolerance provided the registrants amend product labels to specify a maximum of two applications per season a 0.5 lb a.i./A/application. However, data are required depicting residues in/on rape forage harvested following two applications of methyl parathion EC at 0.5 lb a.i./A/application. Alternatively, the registrant can amend product labels to specify applications only to canola, in which case, data on forage will not be required.	Cheminova will amend its labels to specify that methyl parathion can be made to canola only in response to a generic label data call in issued with the RED.
- Rice	No data are required. The data already submitted by Cheminova is sufficient (MRID 41596205)	Cheminova agrees.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
- Rye	No data are required. Processing data from wheat grain will be translated to determine the need for tolerances in processed commodities of barley grain, oat grain, and rye grain.	Cheminova agrees.
- Safflower seed	No data are required; use of methyl parathion on this commodity is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Sorghum	Sorghum grain processing data are not required at the present time. The requirement for a processing study on sweet sorghum will be waived provided the registrants amend their product labels to prohibit uses on sweet sorghum under the label directions for sorghum.	Cheminova will no longer support the use of methyl parathion on sorghum. Cheminova will amend its product labels to remove sorghum in response to a generic label data call-in issued with the RED.
- Soybeans	No data are required. The data already submitted by Cheminova are sufficient (MRID 42690001). A second Cheminova study (MRID 41517104) is also referenced by EPA.	Cheminova agrees.
- Sugar beets	No data are required. The data already submitted by Cheminova are sufficient (MRID 41379306).	Cheminova agrees.
- Sugarcane	No data are required; use of methyl parathion on this commodity is not being supported, per the registrants' responses to the 4/10/97 DCI; the associated tolerance should be revoked.	Cheminova agrees that this crop is not being supported and will not object to EPA revoking this tolerance.
- Sunflower seed	Data are required depicting the potential for the concentration of methyl parathion residues of concern in sunflower meal and oil processed from sunflower seeds bearing detectable residues.	In the 4/10/97 DCI, EPA required a processing study to determine residues of parent and oxon on/in sunflower meal, hulls, crude oil, and refined oil. This study is in progress.
- Wheat	No data are required. The data already submitted by Cheminova are sufficient (MRID 41596209).	Cheminova agrees.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
860.1480: Meat Milk Poultry Eggs		
- Milk and the Fat, Meat, and Meat Byproducts of Cattle, Goats, Hogs, Horses, and Sheep	A ruminant feeding study is required.	In its 90-day response to the DCI, Cheminova agreed to conduct the required cattle and poultry feeding studies. Cheminova stated its intention to submit protocols to the Agency for review prior to initiating the studies and stated that it would like to discuss with EPA the need to analyze animal products for *p*-aminophenol and *p*-nitrophenol. Cheminova submitted the draft study designs to EPA in a letter dated 10/27/98; to date there has been no response to the letter from EPA. However, new issues have arisen with respect to the selection of study analytes and feeding levels. Regarding the recent conclusions from EPA's metabolism committee decision that these studies must include analysis for p-nitrophenol and amino-paraoxon-methyl, Cheminova believes there is no reason to analyze for p-nitrophenol but will attempt to analyze for amino-paraoxon-methyl. In the absence of further communication from EPA on the design of the livestock feeding studies, Cheminova thus plans to analyze samples in these studies for methyl parathion, methyl paraoxon, and, if possible, amino-paraoxon-methyl. Feeding levels will be recalculated after completion of the ongoing field trials on livestock feed items.
- Eggs and the Fat, Meat, and Meat Byproducts of Poultry	A poultry feeding study is required.	In its 90-day response to the DCI, Cheminova agreed to conduct the required cattle and poultry feeding studies. Cheminova stated its intention to submit protocols to the Agency for review prior to initiating the studies and stated that it would like to discuss with EPA the need to analyze animal products for *p*-aminophenol and *p*-nitrophenol. Cheminova submitted the draft study designs to EPA in a letter dated 10/27/98; to date there has been no response to the letter from EPA. Regarding the recent conclusions from EPA's metabolism committee decision that these studies must include analysis for p-nitrophenol and amino-paraoxon-methyl, Cheminova believes there is no reason to analyze for p-nitrophenol but will attempt to analyze for amino-paraoxon-methyl. In the absence of further communication from EPA on the design of the livestock feeding studies, Cheminova thus plans to analyze tissue samples in these studies for methyl parathion, methyl paraoxon, and, if possible, amino-paraoxon-methyl.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Cheminova's Response
860.1400: Water, Fish, and Irrigated Crops	The draft Science Chapter lists this requirement as not applicable to methyl parathion.	Cheminova agrees.
860.1460: Food Handling	The draft Science Chapter lists this requirement as not applicable to methyl parathion.	Cheminova agrees.
860.1850: Confined Rotational Crops	Confined rotational crop data are required. Confined rotational crop data (MRID 43127609) were submitted to satisfy the requirements and are under review.	Cheminova agrees and requests a copy of EPA's review when available.
860.1900: Field Rotational Crops	The need for field rotational crop data will be determined once the confined rotational crop data (MRID 43127609) have been reviewed.	Cheminova has no comment at this time.

Table D-2. Residue Chemistry Data Requirements for the Mcap Formulation and Elf Atochem's Response

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Elf Atochem's Response
860.1200: Directions for Use	The registrant must amend all end-use product labels to specify a minimum spray volume of 2 gallons per acre for vegetable crops and 10 gallons per acre for orchard crops unless they specifically wish to support ULV applications of methyl parathion to crops (other than cotton).	Elf Atochem wishes to keep the option of ULV application of the Mcap formulation to vegetable crops. The minimum spray volume of 10 gallons per acre is acceptable for orchard crops; Elf Atochem will amend its end-use labels accordingly in response to a generic label data call-in issued with the RED.
860.1380: Storage Stability Data-Plant Commodities	Data depicting the storage stability of methyl parathion residues of concern in/on a representative fruit are required.	In response to the 4/10/97 DCI, Elf Atochem committed to submitting the required storage stability data for representative fruit. Elf Atochem has already submitted peach storage stability data (MRID 44413301) and grape storage stability data (MRID 44413403) which are currently under review.
860.1500: Magnitude of the Residue Crop Field Trials		
Potatoes	No data are available to support the use of the Mcap formulation of methyl parathion on potatoes. Data are required depicting methyl parathion residues of concern in/on potatoes harvested 5 days following the last of multiple foliar applications of the Mcap formulation of methyl parathion at 1.5 lb a.i./A/application.	Elf Atochem, in its response to the 4/10/97 DCI, proposed to generate and submit data to the EPA regarding the use of the Mcap formulation of methyl parathion on potatoes. The proposed label rate is 6 applications/season at a rate of 1.5 lb a.i./A/application with a PHI of 5 days.
Sweet potatoes	Data are required depicting methyl parathion residues of concern in/on sweet potatoes harvested 5 days following the last of eight foliar applications of the Mcap formulation of methyl parathion at 0.75 lb a.i./A/application. Alternatively, potato field trial data generated using the Mcap formulation of methyl parathion may be translated to sweet potatoes.	Elf Atochem proposes to conduct potato field trials using the Mcap formulation of methyl parathion and translate the data to sweet potatoes.
Yams	No residue data are required. Furthermore, since a tolerance for residues of methyl parathion is currently established in/on sweet potatoes, a tolerance for residues of methyl parathion in/on yams is not required.	No action required.
Onions	No data are available to support the use of the Mcap formulation of methyl parathion on onions.	Elf Atochem proposes to conduct residue studies on onions at maximum rates of 6 applications at 1 lb a.i./A/application with a PHI of 15 days.
Beans, dried	The available dried bean residue data are adequate, provided the registrant amends the Mcap label to specify a maximum of six applications to dried beans per season along with the currently specified 15-day PHI. A separate tolerance should be established for residues of methyl parathion in/on dried	Elf Atochem proposes to amend the Mcap label for dried beans in response to a generic label data call in issued with the RED. The proposed use rate is 1 lb a.i./A/application with a maximum of 6 applications and a 15-day PHI.

	bean seeds; the available data would support a tolerance of 0.05 ppm for residues of methyl parathion in/on dried bean seed.	

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Elf Atochem's Response
Beans, succulent	The available succulent bean residue data are adequate, provided the registrant amends the Mcap product label to specify a minimum PHI of 7 days. A separate tolerance should be established for residues of methyl parathion in/on succulent beans; the available data would support a tolerance of 1 ppm for residues of methyl parathion in/on succulent beans. The available succulent bean residue data are not adequate to support existing Special Local Needs (SLN) registrations in MN (MN97000100), WI (WI95000500), and MO (MO95000100) for the use of the Mcap formulation of methyl parathion on succulent beans.	Elf Atochem proposes to amend the Mcap label for succulent beans. The proposed use rate is 1 lb a.i./A/application with a maximum of 6 applications and a 7-day PHI (14-day PHI for California). Elf Atochem has submitted study number BR-94-07 (MRID 43967301) to support these SLN registrations. In addition, Elf Atochem will submit a snap bean processing (canning) study (Study Number KP-97-15) to further support these SLN registrations.
Lentils	Provided the registrant amends the Mcap product label to specify a maximum of 3 applications per season at 0.5 lb a.i./A/application to lentils with a 14-day PHI, the available data are adequate and support lowering the tolerance for residues of methyl parathion in/on lentil seeds from 1 ppm to 0.05 ppm. Once this use is included on the Section 3 Registration, existing 24C Registrations in ID (ID84001000) and WA (WA82005400) would no longer be needed and should be canceled.	Elf Atochem proposes to amend the Mcap product label for lentils in response to a generic label data call in issued with the RED. The proposed use rate is 0.5 lb a.i./A/application with a maximum of 3 applications per season and a 14-day PHI.
Peas, succulent, dried	The available pea data (succulent and dried) are adequate and support the establishment of separate tolerances for residues of methyl parathion in/on dried pea seeds at 0.5 ppm and in/on succulent peas at 1 ppm.	Elf Atochem has submitted an amended Mcap label to prohibit use on field peas (Austrian winter peas).
Soybeans	Data are required depicting methyl parathion residues of concern in/on soybeans harvested 20 days following the last of 2 applications of the Mcap formulation of methyl parathion at 1 lb a.i./A/application. In addition, if the required soybean field trials find quantifiable residues in/on soybeans, then data must be submitted for soybean aspirated grain fractions at the maximum label use rate.	Elf Atochem study number BR-91-09 will be submitted to support a proposed label rate of two applications/season at a rate of 1 lb a.i./A/application with a PHI of 30 days. A soybean aspirated grain fractions study is ongoing.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Elf Atochem's Response
Beans, forage and hay	Bean vines and hay are no longer listed as RACs of bean. The only bean species having foliage RACs is cowpea, for which forage and hay are RACs. No bean forage or hay data are available to support the use of the Mcap formulation on cowpeas. The registrant of the Mcap formulation must either (i) amend the use pattern for beans to exclude applications to cowpeas or (ii) provide adequate residue data for cowpea forage and hay.	Elf Atochem proposes to amend the Mcap label to exclude applications to cowpeas in response to a generic label data call in issued with the RED.
Peas, vines and hay	Peas vines and hay are no longer listed as RACs of pea. The registrants must either (i) amend the use pattern for peas to exclude applications to field peas grown for livestock feed or (ii) propose tolerances for field pea vines and hay.	Elf Atochem, in response to the methyl parathion 4/10/97 DCI, committed to amend the Mcap product label to prohibit use on field peas (Austrian winter peas) in response to a generic label data call in issued with the RED.
Soybean, forage, hay	Data are required depicting methyl parathion residues of concern in/on soybean forage and hay reflecting the maximum use rate for the Mcap formulation. Alternatively, if the registrant amends the product label to prohibit feeding of treated soybean forage and hay to livestock, then residue data will not be required and associated tolerances should be revoked.	Elf Atochem will amend the product label to prohibit feeding of treated soybean forage and hay to livestock in response to a generic label data call in issued with the RED.
Tomatoes	Provided the registrant amends the Mcap formulation product label to specify a maximum of five applications/season, the available data are adequate and support lowering the tolerance for residues of methyl parathion in/on tomatoes from 1 ppm to 0.5 ppm.	Elf Atochem will amend the Mcap label to specify a maximum of 5 applications per season on tomatoes in response to a generic label data call in issued with the RED.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Elf Atochem's Response
Apples	New apple field trial data are required depicting methyl parathion residues of concern in/on apples reflecting the maximum use rate of the Mcap formulation of methyl parathion on apples.	Elf Atochem apple field trial data have been submitted (MRIDs 44413501 and 44413502) and are currently under review at the Agency.
Pears	Data are required depicting methyl parathion residues of concern in/on pears resulting from the maximum use rate of the Mcap formulation of methyl parathion on pears.	Elf Atochem proposes to translate apple data to support the use on pears.
Cherries	Data are required depicting methyl parathion residues of concern in/on sweet and sour cherries resulting from the maximum use rate of the Mcap formulation of methyl parathion on cherries.	Elf Atochem has submitted studies BR-92-28 and BR-92-31 (MRIDs 44622501 and 44622502, respectively) in support of the use of the Mcap formulation of methyl parathion on cherries.
Nectarines	The tolerance for residues of methyl parathion in/on peaches will cover residues of methyl parathion in/on nectarines.	No action required.
Peaches	The available data are adequate and support the established 1 ppm tolerance for residues of methyl parathion in/on peaches, provided the registrant amends the Mcap formulation product label to specify a PHI of 21-days for applications at $\leq$ 0.75 lb a.i./A/application and a PHI of 30 days for applications at > 0.75 lb a.i./A/application.	Elf Atochem proposes to amend the Mcap label for peaches in response to a generic label data call in issued with the RED.
Plums (fresh prunes)	Data are required depicting methyl parathion residues of concern in/on plums/fresh prunes reflecting the maximum use rate of the Mcap formulation of methyl parathion on plums.	Elf Atochem study numbers BR-93-07 and BR-93-19 will be submitted to support a proposed label rate of four applications/season at a rate of 1.5 lb a.i./A/application with a PHI of 15-days.
Almonds	Data are required depicting methyl parathion residues of concern in/on almonds and almond hulls reflecting the maximum use rate of the Mcap formulation of methyl parathion on almonds.	Elf Atochem has submitted study BR-93-06 (MRID 44632601) in support of the use of the Mcap formulation of methyl parathion on almonds.
Pecans	Data are required depicting methyl parathion residues of concern in/on pecans reflecting the maximum use rate of the Mcap formulation of methyl parathion on pecans.	Elf Atochem has submitted study BR-88-57 (MRID 43760901) in support of the use of the Mcap formulation of methyl parathion on pecans.
Walnuts	Data are adequate to support the currently established SLN for the use of methyl parathion on walnuts in CA (CA97002400) and indicate that the currently established tolerances for residues of methyl parathion in/on walnuts should be lowered from 0.1 ppm to 0.05 ppm.	No action required.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Elf Atochem's Response
Aspirated grain fractions	Data are required depicting methyl parathion residues of concern in aspirated grain fractions (grain dust) derived from field corn, grain sorghum, soybeans, and wheat grain harvested at the appropriate PHIs following treatment at the maximum labeled rates.	Elf Atochem currently has ongoing wheat and soybean aspirated grain fractions studies. Sorghum is not being supported by Elf Atochem. For all but a single sample, there were no quantifiable residues of methyl parathion found on corn grain. The residues found on this sample were lower than the highest residues found on either the wheat or soybean grain samples by a factor of more than 3X. Therefore, Elf Atochem will establish a tolerance on aspirated grain fractions from either the wheat or soybean studies in progress.
Barley	Residue data on wheat grain, forage, hay, and straw will be translated to support uses on barley (grain, hay, and straw), oats (grain, forage, hay, and straw), and rye (grain, forage, and straw).	No action required.
Corn	The available data are adequate and support the establishment of separate tolerances for residues of methyl parathion in/on sweet corn, field corn grain, and popcorn grain at 0.2 ppm. The registrant should amend all labels to specify the minimum PHIs and maximum single and seasonal use rates supported by the available data.	Elf Atochem proposes to submit an amended label for the Mcap formulation of methyl parathion in response to a generic label data call in issued with the RED.
Oats	Residue data on wheat grain, forage, hay, and straw will be translated to support uses on barley (grain, hay, and straw), oats (grain, forage, hay, and straw), and rye (grain, forage, and straw).	No action required.
Rice	Available data are adequate and indicate that the currently established tolerance for residues of methyl parathion in/on rice should be increased from 1 ppm to 3 ppm. The registrant must amend the Mcap formulation product label to specify a maximum seasonal use rate.	Elf Atochem proposes to amend the Mcap product label for rice in response to a generic label data call in issued with the RED. The proposed use rate is 0.75 lb a.i./A/application with a maximum of 6 applications per season and a 15-day PHI.
Wheat	The available data are adequate to support the use of the Mcap formulation of methyl parathion on wheat, provided the registrant amends the Mcap product label to specify a maximum of 3 applications per season on wheat.	Elf Atochem will amend the Mcap label to specify a maximum of 3 applications per season on wheat in response to a generic label data call in issued with the RED.
Barley, hay and straw	Residue data on wheat grain, forage, hay, and straw will be translated to support uses on barley (grain, hay, and straw), oats (grain, forage, hay, and straw), and rye (grain, forage, and straw).	No action required.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Elf Atochem's Response
Corn, forage and stover	The available data are adequate and indicate that the currently established tolerance for residues of methyl parathion in/on corn forage should be increased from 1 ppm to 20 ppm based on the highest residue level found in forage (18.86 ppm) from study (MRID 41717805) conducted at the maximum use rate for the Mcap formulation of methyl parathion on sweet corn and reflecting a 0-day PHI.	Elf Atochem is not supporting a 0-day PHI on sweet corn forage. Elf Atochem has submitted a amended label for the Mcap formulation of methyl parathion prohibiting the cutting of sweet corn for forage or grazing within 12 days of application.
Oat, forage, hay, straw	Residue data on wheat grain, forage, hay, and straw will be translated to support uses on barley (grain, hay, and straw), oats (grain, forage, hay, and straw), and rye (grain, forage, and straw).	No action required.
Rice, straw	The available rice straw data are not adequate to support the use of the Mcap formulation of methyl parathion on rice.	Based on the DCI statement that no data on rice straw are available reflecting application using ground equipment, Elf Atochem stated in its response to the DCI that there should not be any requirement for additional studies evaluating ground applications because all applications of the Mcap formulation of methyl parathion are made using aircraft.
Wheat, forage, hay, straw	The available data are not adequate to support the use of the Mcap formulation of methyl parathion on wheat. Data are required depicting methyl parathion residues of concern in/on wheat forage, hay, and straw harvested 15 days following the last of three foliar applications of an Mcap formulation of methyl parathion at 0.75 lb a.i./A/application.	Elf Atochem has submitted the following studies to support the use of the Mcap formulation of methyl parathion on wheat: Study Number BR-88-54 (MRID 41818502) and Study Number BR-88-53 (MRID 41560001). Elf Atochem will be submitting the following studies to further support registrations on wheat: BR-88-55, BR-88-56, and BR-95-02.
Grass, forage and hay	Provided the registrant (Elf Atochem) amends their Mcap product label to delete "rangeland, pasture, grass grown for seed production, and roadside areas," as they committed to do in their 90-Day Response to the Methyl Parathion DCI, residue data on grass treated with the Mcap formulation of methyl parathion are not required.	Elf Atochem has submitted a label amendment to delete these uses.
Alfalfa (fresh), hay	New alfalfa field trials are required depicting methyl parathion residues of concern in/on alfalfa seed, alfalfa forage, and alfalfa hay reflecting the maximum use rates of the Mcap formulation of methyl parathion on alfalfa.	Elf Atochem is not supporting the use of the Mcap formulation of methyl parathion on this crop.

Data Requirement	EPA's Conclusions in the Draft Residue Chemistry Chapter of the RED	Elf Atochem's Response
Cottonseed, and gin byproducts	Available data indicate the currently established tolerance for residues of methyl parathion in/on cottonseed should be increased from 0.75 ppm to 5 ppm. The registrant must amend the Mcap formulation product label to specify a maximum seasonal use rate supported by available data. In addition, residue data on cotton gin byproducts are required.	Elf Atochem proposes to amend the Mcap product label for cotton in response to a generic label data call in issued with the RED. The proposed use rate is 1 lb a.i./A/application with a maximum of 8 applications per season and a 14-day PHI. A cotton gin byproducts study is currently in progress.
Grapes	Available data are adequate and indicate that the currently established tolerance for residues of methyl parathion in/on grapes should be increased from 1 ppm to 3 ppm.	In its response to the DCI, Elf Atochem proposed to amend the Mcap product label to lower the maximum application rate to 1 lb a.i./A/application with a maximum of two applications per season and a PHI of 28 days. Uses in California are restricted to postharvest, dormant, and prebloom applications only. Studies BR-94-04 and BR-94-05 have been submitted (MRIDs 44413401 and 44413402, respectively) to support this use. The tolerance should remain at 1 ppm.
Peanuts	Data are required depicting methyl parathion residues of concern in/on peanuts reflecting the maximum use rate of the Mcap formulation of methyl parathion on peanuts. In addition, the registrant must amend the Mcap product label to specify a maximum use rate supported by the residue data. A peanut processing study is also required to support the use of the Mcap formulation of methyl parathion on peanuts.	Elf Atochem has submitted the following studies to support the use of the Mcap formulation of methyl parathion on peanuts: BR-88-58 (MRID 44620302) and BR-95-03 (MRID 44620301). The following peanut processing study was also submitted, BR-88-59 (MRID 44620303). As per Elf Atochem's DCI response, the proposed use rate is 1 lb a.i./A/application with a maximum of 4 applications per season and a 15-day PHI. Feeding restrictions will be proposed for peanut hay.
Plums/prunes, processed food	Data are required depicting the potential for the concentration of methyl parathion residues of concern in/on prunes processed from plums bearing detectable residues.	Elf Atochem study number BR-93-19 will be submitted to support the use of the Mcap formulation of methyl parathion on plums/prunes.

Table D-3: Comments on EPA's Table C. Tolerance Reassessment Summary for Methyl Parathion

Cheminova and Elf Atochem agree with EPA's assessment of the need for tolerances for all commodities listed in Table C of EPA's Tolerance Reassessment Summary for Methyl Parathion except as listed below.

Commodity	Cheminova's and Elf Atochem's Comments
Alfalfa, fresh	Cheminova will submit new data in response to the April 10, 1998, DCI. Elf Atochem is not supporting the use of its Mcap formulation on this crop.
Alfalfa, hay	Cheminova will submit new data in response to the April 10, 1998, DCI. Elf Atochem is not supporting the use of its Mcap formulation on this crop.
Alfalfa, seed	This tolerance should be revoked. It is not required because Cheminova and Elf Atochem are not supporting the use of methyl parathion on alfalfa grown for seed.
Almonds	Elf Atochem has recently submitted data to support the use of the Mcap formulation on this crop. Cheminova is not supporting the use of the EC formulation on this crop.
Almonds, hulls	Elf Atochem has recently submitted data to support the use of the Mcap formulation on this crop and is proposing the establishment of a 25 ppm tolerance for almond hulls. Cheminova is not supporting the use of the EC formulation on this crop.
Apples	Elf Atochem has recently submitted new residue data to support the use of the Mcap formulation on apples. Cheminova is not supporting the use of the EC formulation on this crop.
Beans, dried seed	In response to the April 10, 1997, DCI, Elf Atochem proposed a tolerance of 1 ppm rather than the 0.05 ppm listed by EPA.
Broccoli Brussels sprouts Cabbage Cauliflower Collards Kale Kohlrabi Mustard greens	Cheminova is not interested in supporting the use on kohlrabi. Cheminova agrees that sufficient data have been submitted to support a Brassica crop group tolerance.
Corn, field, grain	Elf Atochem has proposed that the tolerance for this matrix be established at 0.5 ppm rather than the 0.2 ppm level listed by EPA.
Corn, forage	Elf Atochem has proposed that the tolerance for this matrix be 10 ppm rather than the 20 ppm listed by EPA.
Corn, pop, grain	Elf Atochem has proposed that the tolerance for this matrix be established at 0.5 ppm rather than the 0.2 ppm level listed by EPA.

Commodity	Cheminova's and Elf Atochem's Comments
Corn, sweet, K + CWHR	Elf Atochem has proposed that the tolerance for this matrix be established at 0.5 ppm rather than the 0.2 ppm level listed by EPA.
Cottonseed	Elf Atochem has proposed that the tolerance for this matrix be 3 ppm rather than the 5 ppm listed by EPA.
Cowpea, forage Cowpea, hay	Cheminova and Elf Atochem are not supporting the use of methyl parathion on this crop grown for animal feed.
Field pea, vines Field pea, hay	Cheminova and Elf Atochem are not supporting the use of methyl parathion on this crop grown for animal feed.
Grapes	Elf Atochem has recently submitted new residue data for the use of the Mcap formulation on grapes. EPA should wait to establish this tolerance until after it has reviewed these new data.
Grass, hay	This commodity was missing from Table C. Studies are in progress with the EC formulation to support a tolerance on this commodity.
Lentils	Elf Atochem has indicated that it will support the use of the Mcap formulation on this crop and has requested that EPA establish a tolerance of 0.05 ppm.
Melons	Cheminova will not submit any data to support this use; however, Cheminova believes that IR-4 is supporting the use of methyl parathion on this crop.
Oats	EPA will translate wheat data to support the use on oats.
Onions	EPA should specify that additional field trial data are needed to support the use of the Mcap formulation on onions. According to Table B in EPA's residue chemistry chapter, sufficient data have been submitted to support the use of the EC formulation on onions.
Peanuts	Elf Atochem will soon submit new residue data to support the use of the Mcap formulation on this crop. Cheminova is not supporting the use of the EC formulation on peanuts.
Pears	Elf Atochem has requested that EPA translate data submitted for apples to support the use of the Mcap formulation on pears.
Peppers	Cheminova will not submit any data to support this use; however, Cheminova believes that IR-4 may be supporting the use of the EC formulation of methyl parathion on this crop.
Plums (fresh prunes)	Elf Atochem has recently submitted new residue data to support this use.
Potatoes	EPA should specify that new data are required for the Mcap formulation only. Sufficient data have been submitted to support the use of the EC formulation on this crop.
Rape, forage	Cheminova and Elf Atochem are not supporting the use of methyl parathion on this crop grown for animal feed.

Commodity	Cheminova's and Elf Atochem's Comments
Rye	A tolerance for rye grain, forage, and straw should be established based on translation of data from wheat. Cheminova has also requested the establishment of a cereal grain crop group tolerance.
Sorghum	Cheminova and Elf Atochem are not supporting the use of methyl parathion on sorghum. Tolerances for grain sorghum grain, fodder, and forage should be revoked.
Sweet potatoes	Cheminova is not supporting the use of the EC formulation of methyl parathion on this crop. However, Elf Atochem holds a 24(c) registration for its Mcap formulation.

Attachment E

Comments on EPA's memorandum titled "Methyl Parathion (054501). The Outcome of the HED Metabolism Assessment Review Committee Meeting Held on March 11, 1998"

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4 pages

METABOLISM

These comments address EPA's memorandum titled "Methyl Parathion (054501). The Outcome of the HED Metabolism Assessment Review Committee Meeting Held on March 11, 1998" (Bonnie Cropp-Kohlligian, May 21, 1998) (EPA Attachment 4) (herein referred to as the "Metabolism Committee Memorandum"). The decisions as stated in the Metabolism Committee Memorandum and Cheminova Agro A/S's (Cheminova's) responses to those decisions are provided below.

I. MAGNITUDE OF THE RESIDUES IN PLANTS

EPA's Position: In the Metabolism Committee Memorandum, EPA requested that analyses of crop samples in future plant magnitude of the residue studies include parathion, methyl paraoxon, and paranitrophenol (PNP). EPA requested crop residue data on PNP so that aggregate exposure from all registered uses of PNP, including its use as a fungicide on leather, can be evaluated.

Cheminova's Response: As is stated in the January 1998 Reregistration Eligibility Decision (RED) for PNP, the sole registrant of PNP, the United States Department of the Army, has requested the cancellation of the registration of this compound. EPA further states in the PNP RED that it has accepted the voluntary cancellation, which will be effective on May 30, 2002. EPA's reasons for accepting this voluntary cancellation further support Cheminova's position that there is no need to analyze methyl parathion treated crops for PNP. EPA's reasons are summarized below:

A. The weight of evidence from all available toxicological data does not suggest a potent threat from dermal or inhalation exposure.

B. Exposure to PNP is very limited and confined to leather and cork treatment applied by military contractors to a few products used by military workers.

C. During the 5-year phase-out period, workers using and handling PNP solutions and freshly treated products are required to wear chemical resistant aprons and attached full sleeve gloves.

Moreover, it is not clear why a registration involving treatment of leather would ever implicate a need for crop residue data for PNP since aggregate risk assessments exclude occupational exposures. Therefore, Cheminova believes that residues of PNP in crops do not need to be determined in future plant magnitude of the residue studies.

II. MAGNITUDE OF THE RESIDUES IN MEAT, MILK, AND EGGS

EPA's Position: In the *Nature of the Residue in Livestock* section, EPA also states that the residues of concern in animal commodities are methyl parathion, methyl paraoxon, PNP, and amino-paraoxon-methyl. As explained in more detail in the Metabolism Committee Memorandum, the metabolism committee tentatively decided that the tolerance expression for methyl parathion in animal commodities consists of methyl parathion only, but that methyl parathion residues of concern to be included in the ChE risk assessment for animal commodities include methyl parathion and methyl paraoxon. The committee also tentatively concluded that methyl parathion residues of overall concern in animal commodities are methyl parathion, methyl paraoxon, PNP, and aminoparaoxon-methyl. The Metabolism Committee memorandum concludes that all four chemical species should be determined in the required livestock feeding studies.

Cheminova's Response: In its April 10, 1997, data call-in (DCI) for methyl parathion, EPA requested that milk, eggs, and livestock tissues be analyzed for methyl parathion, methyl paraoxon, and free and conjugated forms of p-aminophenol and PNP. In response to this DCI, Cheminova submitted proposed testing designs for this study on October 27, 1997, in which it proposed to analyze livestock study tissues for methyl parathion and methyl paraoxon only. The Metabolism Committee Memorandum requires analysis of livestock tissue for free PNP, in addition to methyl parathion and methyl paraoxon; however, analysis for aminoparaoxon-methyl is now also required.

Cheminova does not believe that animal commodities need to be analyzed for PNP. From a toxicological point of view, PNP does not contain the active phosphorus moiety of methyl parathion and therefore does not inhibit ChE. Available information on the toxicity of PNP indicates that its toxicity is much lower than the ChE-inhibiting toxicity associated with methyl parathion. In addition, PNP lies on the excretory pathway for methyl parathion in animals. Finally, as noted above, EPA states in the PNP RED that it has accepted the U.S. Army's voluntary cancellation for the sole remaining use of PNP as an active ingredient. Therefore, there is no need to obtain residue data for PNP in livestock because there is no need for an aggregate risk assessment for PNP as an active ingredient.

With regard to aminoparaoxon-methyl, Cheminova believes that EPA's new request to analyze livestock tissues for this metabolite is reasonable, although EPA indicates that its concern is based on neuropathy of unknown origin and not due to ChE inhibition. However, because aminoparaoxon-methyl is likely to be water soluble, and because there is little or no available analytical experience with this metabolite, Cheminova

believes that its analyses in livestock tissues will be difficult. However, Cheminova will attempt to analyze tissues from the cattle and poultry feeding studies for this metabolite.

In the absence of further communication from EPA on the design of the livestock feeding studies, Cheminova thus plans to analyze tissue samples in these studies for methyl parathion, methyl paraoxon, and, if technically possible, aminoparaoxon-methyl.

Attachment F
Exposure

Comments on EPA's March 2, 1998, memorandum titled "Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Methyl Parathion."

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13 pages
EXPOSURE

Cheminova Agro A/S (Cheminova) is commenting on EPA's March 2, 1998, memorandum titled "Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Methyl Parathion." This document contains the Agency's draft occupational exposure assessment for methyl parathion. Cheminova's comments on specific points in EPA's draft document are provided below.

I. TITLE OF THE RISK ASSESSMENT

The Agency's document is titled "Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Methyl Parathion." Cheminova believes that this title is misleading because there are no supported residential uses of methyl parathion. Cheminova believes that EPA should delete the term "residential" from the title of this chapter.

II. TOXICITY ENDPOINT SELECTION

Cheminova believes that EPA calculated the margins of exposure (MOEs) for the occupational risk assessment using inappropriate toxicity endpoints. Specifically, Cheminova believes that the following no observed effect levels (NOELs) should be used:

short-term = 0.1 mg/kg bw/day; and
intermediate-term = 0.1 mg/kg bw/day.

Cheminova's position is further explained in Section IV of Attachment A and Section IV of Attachment B.

III. DERMAL ABSORPTION

EPA is proposing a 100% default for dermal absorption to calculate the MOEs, based on the lack of confidence by the Agency in a much lower percentage of dermal absorption predicted based on a 21-day rabbit dermal study of methyl parathion (Goad, 1992; MRID 42263701).

A 100% default is overly conservative. EPA appears to base the default on the absence of a "valid" dermal study, and on one set of LD_{50} data which show similar LD_{50}s for oral and dermal administration. However, it is not known whether oral exposure to the test material was precluded in the dermal LD_{50} study included in the Hazard Identification Committee (HID) review. There are other data that may be used

to more accurately estimate dermal absorption. For example, as shown in Tables F-1 and F-2, a comparison of rat dermal and oral LD_{50} data for both the technical product and the emulsifiable concentrate formulation show at least a 10-fold difference in lethality between oral and dermal routes. (Note: The SafePharm acute study reports used as the basis for this table are being submitted to EPA).

Table F-1. Comparison of Acute LD_{50}s for Oral and Dermal Application to Rats

Year	Report No.	Formu-lation	% a.i.	Laboratory	Rat Strain	Route	Vehicle	Dose (mg/kg)	
								Male	Female
1993	545/7	EC	47.1	SafePharm	S-D	Oral	Distilled Water	10; 16; 25; 63	10; 16; 25; 63
1993	545/8	EC	47.1	SafePharm	S-D	Dermal	Distilled Water	500; 1,000; 2,000	500; 1,000; 2,000
1986	34117/ 34	TC	79.2	IRI	S-D	Oral	Corn Oil	20; 30; 40	40; 70; 100
1986	34117/ 34	TC	79.2	IRI	S-D	Dermal	None	400; 500; 600	400; 500; 600

Table F-2. Comparison of Acute LD_{50}s for Oral and Dermal Application to Rats

Year	Report No.	Dosing Volume		Males			Females			Method for LD_{50} Calculation
				LD_{50} mg/kg b.w.			LD_{50} mg/kg b.w.			
		Route	mL/kg b.w.	LD_{50}	>	<	LD_{50}	>	<	
1993	545/7	Oral	10.0	33	23	48	28	18	43	Dreher
1993	545/8	Dermal	10.0	561	232	1,360	1,682	1,091	2,594	Dreher
1986	34117/ 34	Oral	10.0	25	21	30	62	47	82	Cuthbert; Carr
1986	34117/ 34	Dermal	—	483	427	546	481	437	529	Cuthbert; Carr

EC = emulsifiable concentrate
TC = technical product
a.i. = active ingredient

From the data in Tables F-1 and F-2, one can conclude that for either the technical product or the emulsifiable concentrate (EC) formulation, the dermal LD_{50} is at least 10 times the oral LD_{50}. Thus, for dermal exposure a dermal absorption factor of 10% should be sufficient. This is protective of humans because rat skin is more permeable than human skin for the majority of compounds tested.

Further, *in vitro* studies using rat skin under worst-case occlusive conditions predict that dermal penetration of methyl parathion does not exceed 25%. Confidence in these *in vitro* data is limited due to the variability of the results; however, the data clearly show, in conjunction with the acute oral and dermal study data, that the extent of dermal penetration of methyl parathion would not approach 100% of the applied dose.

Thus, a default absorption of 10% to 25% provides a more justifiable estimate of dermal penetration in rats than the 100% default used by EPA. These data also correlate with dermal penetration estimates developed for the closely structurally related compound ethyl parathion. It should be noted that Cheminova is currently developing dermal study data to more clearly define the NOELs for cholinesterase inhibition, clinical signs, and potential neuropathology from short-term duration dermal exposures.

IV. SAFETY FACTORS

Cheminova believes that there is an error in the target safety factor used for this risk assessment. On page 4 of EPA's document, the Agency states that it included an additional 10X safety factor in its occupational risk assessment in accordance with the Food Quality and Protection Act (FQPA); therefore, EPA lists the target MOE for acceptable occupational risk as 1,000. However, Cheminova notes that the September 1, 1998, draft Health Effects Division Chapter states that the extra 10X is <u>not</u> to be retained for occupational or residential exposure. In addition, on page 10 of EPA's document, the Agency states that "an MOE of ó100 is needed in the occupational risk assessment since the Agency does not consider it appropriate to apply the FQPA safety factor to occupationally exposed workers" (Special Report of the FQPA Safety Factor Committee, April 15, 1998). Thus, the target MOE for acceptable occupational risk is 100.

V. EXPOSURE SCENARIOS AND ASSUMPTIONS IN EPA's RISK ASSESSMENTS

Cheminova believes that EPA calculated MOEs for exposure scenarios that are no longer supported. Relevant input parameters for the occupational risk assessments and specific concerns (if applicable) raised by EPA are discussed below.

PERSONAL PROTECTIVE EQUIPMENT

Methyl parathion may only be used in accordance with the requirements of the EPA's Worker Protection Standard (WPS) defined in 40 CFR part 170. This standard contains requirements for the protection of agricultural workers and handlers of agricultural pesticides. As specified on Cheminova's labels, and in accordance with the WPS requirements, any person using methyl parathion must use the following personal protective equipment:

- coveralls over long-sleeved shirt and long pants;
- chemical-resistant apron;
- chemical-resistant gloves;
- chemical-resistant footwear plus socks;
- chemical-resistant headgear;
- protective eyewear; and
- an MSHA/NIOSH approved respirator.

ENGINEERING CONTROLS

In December 1996, Cheminova and other "active" EC registrants (i.e., those formulators of EC end-use products with whom Cheminova had supply agreements) signed an agreement ("the December 1996 Agreement") with EPA that was designed to reduce the chance of misuse of methyl parathion products. Per the December 1996 Agreement, all EC formulations are packaged only in returnable-refillable containers with a tamper-resistant mechanism that does not permit removal of material without specialized equipment.

REENTRY INTERVAL

A 48-hour restricted entry interval is in place for methyl parathion. Workers are prohibited from entering a treated field within the 48-hour restricted entry interval. In accordance with the provisions of the WPS, entry into treated fields is permitted within 48 hours only with the use of the personal protection equipment listed above.

SUPPORTED FORMULATIONS

EPA states that methyl parathion is formulated as a granular (0.2% active ingredient), a microencapsulate (20.9% active ingredient), and an emulsifiable

concentrate (ranges from 11.2% to 70.74% active ingredient). Cheminova notes that it is not supporting any granular formulations and that the December 1996 Agreement prohibits any EC formulations that contain greater than 5.0 lb of active ingredient per gallon of formulation. Cheminova believes that the Agency should have canceled all granular formulations and any EC formulation containing more than 5.0 lb a.i. per gallon of formulation.

EPA states that methyl parathion is formulated with several other active ingredients, including malathion, endosulfan, ethyl parathion, and permethrin. Cheminova is only supporting the Ethyl-Methyl 6-3 EC formulation.

SUPPORTED APPLICATION METHODS

EPA states that methyl parathion may be applied aerially and by airblast sprayer, chemigation, ground-boom, and tractor-drawn granular spreaders. EPA claims that certain methods of application pose a potential for worker exposure to methyl parathion. EPA specifically mentions that it has concerns related to the application scenarios discussed below; Cheminova's responses are provided.

Mixing/Loading: Cheminova believes that the combination of engineering controls and required personal protective equipment significantly reduce the potential for mixer and/or loader exposure to the EC formulations of methyl parathion. Although the encapsulated (Mcap) formulation does not have to comply with the engineering controls required for the EC formulations, the Mcap formulation is engineered to have a lower rate of dermal absorption, thereby reducing the potential of exposure to workers during mixing/loading.

Aerial applications made using less than two gallons of finished spray per acre: With the exception of aerial application to grass and cotton, Cheminova is not supporting any aerial application of methyl parathion made in solutions of less than two gallons of finished spray per acre. Cheminova will amend its end-use labels accordingly. Elf Atochem is supporting aerial applications of the Mcap formulation in less than two gallons of finished sprays. The Mcap formulation label allows one gallon of finished product per acre in corn. Elf Atochem has informed Cheminova that the 10 gallon per acre minimum for orchards is acceptable.

Chemigation: Cheminova is not supporting the application of the EC formulation through any type of irrigation system and has included language on their end use labels specifically prohibiting this application method. Chemigation is currently allowed only for the Mcap formulation registered to Elf Atochem.

4. Use of human flaggers: Cheminova is not supporting the use of human flaggers during aerial application of the EC formulation of methyl parathion and has included language on its end-use labels to prohibit the use of human flaggers application method. The use of human flaggers is currently allowed only for Mcap formulation registered by Elf Atochem.

SUPPORTED USES

On pages 2 and 3 of the draft Occupational Exposure Chapter, EPA summarizes the uses for which it believes methyl parathion can be applied. Cheminova believes that there are numerous errors in EPA's lists. Each of the use categories mentioned by EPA is discussed below.

Forage, feed, and fiber crops: The use of methyl parathion is not being supported for the following crops included in EPA's list: clover, cucumber, gooseberries, kohlrabi, lentils, rutabaga, sorghum, tobacco, and vetch. Cheminova understands that IR-4 may be supporting the use on hops. Elf Atochem is supporting a 24(c) registration of the Mcap formulation on sweet potatoes/yams.

Fruits and nuts: The uses included in EPA's list appear to be correct; however, Cheminova notes that all fruit and nut uses are supported for the Mcap formulation only. The use of the EC formulation on these crops is not supported.

Ornamental Plants and Forest Trees: Cheminova is not supporting the use of methyl parathion on any of the uses listed in this category.

Nonagricultural land, pastures: Cheminova is supporting the use of the EC formulation on grasses.

Rice: Cheminova is not supporting the use of methyl parathion on rice to control mosquitoes. The use of methyl parathion on rice is for the control of insect pests that may damage the rice crop.

ASSESSMENT OF OCCUPATIONAL EXPOSURE USING PESTICIDE HANDLERS EXPOSURE DATABASE

As stated in Section B of this Attachment, Cheminova believes that the following NOELs should be used:

short-term = 0.1 mg/kg bw/day; and
intermediate-term = 0.1 mg/kg bw/day

Cheminova reran EPA's assessment using these more appropriate NOELs and obtained the MOEs shown in the following tables (Tables F-3 and F-4).

Table F-3. (Revision to EPA's Table 2).
Occupational Short-Term Combined Inhalation and Dermal MOEs for Methyl Parathion with Mitigation Measures for Occupational Exposures

Exposure Scenario (Scenario #)	Mitigation Measures					
	Engineering Controls					
	Unit Dermal Exposure (mg/lb ai)	Daily Dermal Dose (mg/kg bw/day)	Unit Inhalation Exposure (mg/lb ai)	Daily Inhalation Dose (mg/kg bw/day)	Total Daily Dose (mg/kg bw/day)	Total MOE
Mixing/Loading Liquids (emulsifiable concentrate) for Aerial Application (1a)	0.009 (gloves)	0.0045	0.08	0.000040	0.0045	22
		0.045		0.00040	0.045	2.2
		0.14		0.0012	0.14	0.71
Mixing/Loading Liquids (emulsifiable concentrate) for Groundboom Application (1b)		0.0010		9.1 E-06	0.0010	100
		0.010		9.1 E-05	0.010	10
		0.031		0.00027	0.031	3.2
Mixing/Loading Liquids (emulsifiable concentrate) for Airblast Sprayer (1c)		0.0051		0.000046	0.0051	19.6
Mixing/Loading Liquids (microencapsulated) for Aerial/Chemigation Application (2a)	0.009	0.045	0.24	0.00040	0.045	2.2
		0.14		0.0012	0.14	0.71
Mixing/Loading Liquids (microencapsulated) for Groundboom Application (2b)		0.01		0.000091	0.01	10
		0.031		0.00027	0.031	3.2
Mixing/Loading Liquids (microencapsulated) for Airblast Sprayer (2c)		0.0051		0.000046	0.0051	19.6

Table F-3 (continued). (Revision to EPA's Table 2).
Occupational Short-Term Combined Inhalation and Dermal MOEs for Methyl Parathion With Mitigation Measures for Occupational Exposures

Exposure Scenario (Scenario #)	Mitigation Measures					
	Engineering Controls					
	Unit Dermal Exposure (mg/lb ai)	Daily Dermal Dose (mg/kg bw/day)	Unit Inhalation Exposure (mg/lb ai)	Daily Inhalation Dose (mg/kg bw/day)	Total Daily Dose (mg/kg bw/day)	Total MOE
Applying Liquids with Fixed-wing Aircraft (4a)	0.005	0.0025	0.068	0.000034	0.0025	40
		0.025		0.00034	0.025	4
		0.075		0.0010	0.076	1.3
Applying Liquids with Helicopter Aircraft (5)	0.0021	0.0011	0.0018	9.0 E-07	0.0011	91
		0.011		9.0 E-06	0.011	9.1
		0.032		2.7 E-05	0.032	3.1
Applying Liquids with a Groundboom Sprayer (6)	0.0067	0.00077	0.043	4.9 E-06	0.00078	128
		0.0077		4.9 E-05	0.0078	12.8
		0.023		0.00096	0.024	4.2
Applying Liquids (microencapsulated) with an Airblast Sprayer (7)	0.016 (gloves)	0.0090	0.4	0.00023	0.0092	10.9

Table F-4. (Revision to EPA's Table 3).
Occupational Intermediate-term Combined Inhalation and Dermal MOEs for Methyl Parathion With Mitigation Measures for Occupational Exposures

Exposure Scenario (Scenario #)	Mitigation Measures					
	Engineering Controls					
	Unit Dermal Exposure (mg/lb a.i.)	Daily Dermal Dose (mg/kg bw/day)	Unit Inhalation Exposure (mg/lb a.i.)	Daily Inhalation Dose (mg/kg bw/day)	Total Daily Dose (mg/kg bw/day)	Total MOE
Mixing/Loading Liquids (emulsifiable concentrate) for Aerial Application (1a)	0.009 (gloves)	0.0045	0.08	0.000040	0.0045	22
		0.045		0.00040	0.045	2.2
		0.14		0.0012	0.14	0.71
Mixing/Loading Liquids (emulsifiable concentrate) for Groundboom Application (1b)		0.0010		9.1 E-06	0.0010	100
		0.010		9.1 E-05	0.010	10
		0.031		0.00027	0.031	3.2
Mixing/Loading Liquids (emulsifiable concentrate) for Airblast Sprayer (1c)		0.0051		0.000046	0.0051	19.6
Mixing/Loading Liquids (microencapsulated) for Aerial/Chemigation Application (2a)	0.009	0.045	0.24	0.00040	0.045	2.2
		0.14		0.0012	0.14	0.71
Mixing/Loading Liquids (microencapsulated) for Groundboom Application (2b)		0.01		0.000091	0.01	10
		0.031		0.00027	0.031	3.2
Mixing/Loading Liquids (microencapsulated) for Airblast Sprayer (2c)		0.0051		0.000046	0.0051	19.6

Table F-4 (continued). (Revision to EPA's Table 3).
Occupational Intermediate-term Combined Inhalation and Dermal MOEs for Methyl Parathion With Mitigation Measures for Occupational Exposures

Exposure Scenario (Scenario #)	Mitigation Measures					
	Engineering Controls					
	Unit Dermal Exposure (mg/lb a.i.)	Daily Dermal Dose (mg/kg bw/day)	Unit Inhalation Exposure (mg/lb a.i.)	Daily Inhalation Dose (mg/kg bw/day)	Total Daily Dose (mg/kg bw/day)	Total MOE
Applying Liquids with Fixed-wing Aircraft (4a)	0.005	0.0025	0.068	0.000034	0.0025	40
		0.025		0.00034	0.025	4
		0.075		0.0010	0.076	1.3
Applying Liquids with Helicopter Aircraft (5)	0.0021	0.0011	0.0018	9.0 E-07	0.0011	91
		0.011		9.0 E-06	0.011	9.1
		0.032		2.7 E-05	0.032	3.1
Applying Liquids with a Groundboom Sprayer (6)	0.0067	0.00077	0.043	4.9 E-06	0.00078	128
		0.0077		4.9 E-05	0.0078	12.8
		0.023		0.00096	0.024	4.2
Applying Liquids (microencapsulated) with an Airblast Sprayer (7)	0.016 (gloves)	0.0090	0.4	0.00023	0.0092	10.9

MOE SECTION POST-APPLICATION

EPA has calculated the MOEs assuming a default of 100% absorption. As discussed previously, based on *in vitro* and *in vivo* rat data, Cheminova believes the dermal absorption of the technical or formulated product to be in the 10% to 25% range.

As discussed previously, Cheminova believes that use of the chronic two-year study of methyl parathion as the basis for *intermediate-term* occupational risk assessment is inappropriate. Cheminova believes that the NOEL of 0.1 mg/kg bw/day, as stated in Attachment B, Section IV.C, is more appropriate for the evaluation of re-entry scenarios.

Based on these assumptions, Cheminova has recalculated EPA's Table 5 (see Table F-5, below). In regard to the original Table 5, Cheminova is uncertain which default values the Agency used to calculate the appropriate dermal dose. Therefore, Cheminova used the values calculated by the Agency, adjusted for 25% dermal absorption, and an NOEL of 0.1 mg/kg bw/day to calculate the MOEs.

Table F-5. **(Revision of EPA's Table 5)**. Methyl Parathion Intermediate-Term Surrogate Post-Application Assessment for Microencapsulated Formulation (Range Finder).

DAT[a]	DFR (µg/cm^2)[b]		Dermal Dose (mg/kg bw/day)[c]		MOE[d]	
	Min Rate	Max Rate	Min Rate	Max Rate	Min Rate	Max Rate
0	0.22	6.7	0.0031	3.83	31.8	0.026
23	0.0003	0.009	0.000004	0.000125	23,333	800
48	NA	6.7 E-06	NA	3.9E-07	NA	1,025,641

NA = Not Applicable

[a] DAT = "days after treatment"

[b] Initial DFR (µg/cm^2) = Application Rate (min 0.1 1b a.i./A; and max 3.0 lb a.i. /A) x Conversion Factor (1 lb a.i./A = 11.209 µ/cm^2) x Fraction of Initial a.i. Retained on Foliage

$$\textit{Daily Dissipation DFR} = AR\left[\frac{\text{lb a.i}}{A}\right] \times (1-\text{daily DFR})^{(1-D)t} \times CF\left[\frac{\text{mg per cm}^2}{\text{lb per A}}\right] \times FI$$

Where: Assumed percent DFR after initial treatment is 20%, and each day after the percent dissipation per day is 25%

[c] Dose = DFR (µg/cm^2) x Transfer Coefficient (min rate 500, max rate 20,000 cm^2/hr) x Conversion Factor
(1 mg/1000 µg) x Dermal Absorption (1) x Hrs Worked Per Day (8 hrs)/ Body Weight (70 kg)

[d] MOE = NOEL (mg/kg/day) / Dermal Dose (mg/kg/day).
Where: intermediate NOEL is 0.1 mg/kg/day.

As stated in Section IV, Cheminova believes that the extra 10X factor should not have been retained for the Agency's post application risk assessments. Thus, Cheminova believes that the target MOE for acceptable risk is 100.

Attachment G

References for Comments on EPA's Methyl Parathion Draft Health Effects Division Chapter of the Reregistration Eligibility Decision Document

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7 Pages

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Exposure

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CONFIDENTIAL ATTACHMENT H

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Financial Sales Information on Methyl Parathion
from
Comments on EPA's Methyl Parathion
Draft Health Effects Division Chapter
of the Reregistration Eligibility Decision Document

DATA REQUIREMENTS

Not Applicable

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STATEMENT OF DATA CONFIDENTIALITY CLAIMS

Information claimed confidential on the basis of its falling within the scope of FIFRA Section 10 has been removed to this confidential attachment, and is cited by cross-reference number in the body of the study.

Cross Reference Number 1 — This cross reference number noted on a place-holder page is used in place of the following whole page at the indicated volume and page reference.

The deleted page is attached immediately behind this page.

PAGE	REASON FOR THE DELETION	FIFRA REFERENCE
35	Financial sales information on methyl parathion	Section 10